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The Use of the Fertilities of Affected Individuals and their Unaffected Sibs in the Estimation of Fitness*

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INTRODUCTION

IN GENETIC WORK, it is often of interest to inquire whether people with a particular affection are more or less fertile than people generally. Ideally, this problem could best be examined by comparing the average fertility of a sample of affected people with the average fertility of some control group carefully chosen so as to be representative of the general population. For practical reasons, however, comparisons of this type are rarely feasible, and the investigator is often confronted with the problem of having no group of normals with which to compare the fertility of affected cases, save their unaffected sibs. It is open to question whether sib comparisons are generally permissible, but if we assume they are it is necessary that the limitations of the approach be clearly understood and that the method of analysis be sensible.

REASON FOR NOT USING MOST OBVIOUS APPROACH

The most obvious way to estimate fitness using affected people and their unaffected sibs is to divide the average number of children per affected person by the average number of children per unaffected sib. However, this practice is fallacious, for insofar as fertility is an inherited trait, we may reasonably expect that persons from large sibships will tend to be more fertile than persons from small sibships with the result that, in a sporadic condition, for example, a sibship of, say, 13, will contribute one comparatively fertile affected and 12 fertile unaffected, while a sibship of size two contributes one comparatively infertile affected and *but one* comparatively infertile unaffected (Krooth, 1953). Thus a sample of two sibships—one of size two and the other of size 13—could lead us to conclude that affected children were less fertile than normal children, when, in fact, no such difference existed. The degree of the distortion produced by this bias in the estimate of fitness will, of course, vary somewhat from data to data.

The methods of analysis to be presented here will allow for the above difficulty and for others. As the methods are developed, it will be seen that in some cases they require discarding certain, not inappreciable, portions of the data. The author has been less concerned to present techniques of high efficiency, than to present techniques requiring a minimum number of assumptions.

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CONDITIONS OF SAMPLING

Single ascertainment

We shall consider that we take a random non-hypergeometric sample of affected children, i.e., that there is single ascertainment (Bailey, 1951). We shall assume that, after the families are ascertained, at least some information is obtained about three generations in each family, namely, about the generation of the affected person through whom the family was ascertained (*"the secondary generation"*), the generation of the parents of the affected person (*"the primary generation"*), and finally the generation of the children of the affected person. It will be assumed that the information available is only sufficient to allow us to make reliable estimates of the mean fertility of persons in the *secondary generation*, and hence both affected sibs and unaffected controls come from this generation. The person through whom the sibship was obtained will be designated the propositus. It will be understood that our *estimate* of fitness is based only on the propositus and his sibs, that is, *not* on more distant relatives in the secondary generation. We shall adopt the convention that when we speak of "sibships in the secondary generation," we are referring only to those sibships which contain a propositus. As we shall subsequently see, since ascertainment is through affected individuals, we shall only be able to extract information about the relative fertility of affecteds who come from sibships of size two or greater. Obviously such information may be misleading, particularly if a large proportion of affecteds come from sibships of one. However, this difficulty is inherent in the use of sibs as controls, and it has to be accepted as a limitation of the approach.

A RARE DOMINANT TRAIT

Let us suppose the affection we are dealing with is a rare dominant condition, so that affected children may come from (1) matings of normal homozygotes who could produce an affected child through mutation, or (2) matings of an affected heterozygote with a normal homozygote. We shall refer to children in the secondary generation who come from type (1) matings as *sporadics* while those from type (2) matings will be designated *familials*.

A. Expressions for fertility and fitness in the general population

Consider now the population from which our series of cases was sampled.

Let θ_r be the proportion in the population of all those sibships in the secondary generations, produced by normal x normal matings in the primary generation, which are of size r.

Let ψ_r be the proportion in the population of all those sibships in the secondary generation, produced by normal x affected matings in the primary generation, which are of size r.

Let Ω = the mean fertility in the population of all people in the secondary generation.

Let Ω' = the mean fertility in the population of all people in the secondary generation which comprise sibships of size two or greater. We shall refer to this quantity as the *partial mean fertility* (PMF) of the population.

Let Ω_r = the mean fertility of unaffected people in the secondary generation from (1) normal x normal matings, and (2) sibships of size r.

Let $\hat{\Omega}_r$ = the mean fertility in the population of affected people in the secondary generation who come from (1) normal x normal matings, and comprise (2) sibships of size r.

Let ω = the mean fertility in the population of affected persons in the secondary generation.

Let ω' = the mean fertility in the population of affected persons in the secondary generation who come from sibships of size two or greater, i.e., the *partial mean fertility* of affected.

Let ω_r = the mean fertility in the population of affected people in the secondary generation who come from (1) normal x affected matings, and (2) sibships of size r.

Let $\hat{\omega}_r$ = the mean fertility in the population of unaffected people in the secondary generation who come from (1) normal x affected matings, and (2) sibships of size r.

Let π = the proportion of normal x affected matings in the primary generation (in the population) and let us *assume* that the condition is sufficiently rare that $(1 - \pi)$ yields, near enough, the corresponding proportion of normal x normal matings.

Let ρ_1 = the proportion of all those children in the population from normal x normal matings who are affected.

Let ρ_2 = the proportion of all those children in the population from abnormal x normal matings who are affected.

Thus, the mean fertility of the whole secondary generation becomes

$$\Omega = \frac{(1-\pi)\left[(1-\rho_1)\sum_{r=0}^{r=\infty} r\theta_r\Omega_r + \rho_1\sum_{r=0}^{r=\infty} r\theta_r\hat{\Omega}_r\right] + \pi\left[(1-\rho_2)\sum_{r=0}^{r=\infty} r\psi_r\hat{\omega}_r + \rho_2\sum_{r=0}^{r=\infty} r\psi_r\omega_r\right]}{(1-\pi)\sum_{r=0}^{r=\infty} r\theta_r + \pi\sum_{r=0}^{r=\infty} r\psi_r}.$$

However, since we are going to estimate the partial mean fertility, we shall be more concerned with Ω' which can be expressed thus:

$$\Omega' = \frac{(1-\pi)\left[(1-\rho_1)\sum_{r=2}^{r=\infty} r\theta_r\Omega_r + \rho_1\sum_{r=2}^{r=\infty} r\theta_r\hat{\Omega}_r\right] + \pi\left[(1-\rho_2)\sum_{r=2}^{r=\infty} r\psi_r\hat{\omega}_r + \rho_2\sum_{r=2}^{r=\infty} r\psi_r\omega_r\right]}{(1-\pi)\sum_{r=2}^{r=\infty} r\theta_r + \pi\sum_{r=2}^{r=\infty} r\psi_r}.$$

Only the limits of summation have changed.

Our supposition that the condition is a rare one enables us to make some simplifying assumptions, namely, that π and ρ_1 are both very small compared with one. We can then write a much more tractable expression for Ω' which, though approximate, will be entirely adequate. We write

$$\Omega' = \frac{\sum_{r=2}^{r=\infty} r\theta_r\Omega_r}{\sum_{r=2}^{r=\infty} r\theta_r}.$$

Let us now develop comparable expressions for the partial mean fertility of affected people. We see that

$$\omega' = \frac{(1-\pi)\rho_1 \sum_{r=2}^{r=\infty} r\theta_r\hat{\Omega}_r + \pi\rho_2 \sum_{r=2}^{r=\infty} r\psi_r\omega_r}{(1-\pi)\rho_1 \sum_{r=2}^{r=\infty} r\theta_r + \pi\rho_2 \sum_{r=2}^{r=\infty} r\psi_r},$$

or

$$\omega' = \frac{(1-\lambda)\sum_{2}^{\infty} r\theta_r\hat{\Omega}_r}{\sum_{2}^{\infty} r\theta_r} + \frac{\lambda\sum_{2}^{\infty} r\psi_r\omega_r}{\sum_{2}^{\infty} r\psi_r},$$

where

$$\lambda = \frac{\rho_2\pi\sum_{2}^{\infty} r\psi_r}{(1-\pi)\rho_1\sum_{2}^{\infty} r\theta_r + \pi\rho_2\sum_{2}^{\infty} r\psi_r},$$

that is, the proportion of all affected children in the secondary generation who have an affected parent, i.e., the proportion of *familials*.

We may define fitness as $\frac{\omega}{\Omega}$ and the partial fitness as $\frac{\omega'}{\Omega'}$.

B. Expressions for fertility and fitness in the sample

We outlined the conditions of sampling at the beginning of Section III. It will be understood that all the quantities defined below are obtained *from the sample.*

We shall first divide the sibships into those which contain a sporadic case and those which contain one or more familial cases, and we shall consider the distribution of sibship sizes in these two groups separately.

Let B_r = the proportion of all those sibships, of size two or greater and containing an affected *sporadic*, which are of size r.

Let b_r = the proportion of all those sibships, of size two or greater and containing one or more affected *familials*, which are of size r.

Let T_r = the proportion of all sibs, in *sporadic* sibships of size r, who were detected.

Let t_r = the proportion of all sibs, in familial sibships of size r, who were detected.

"Detected" is here used to denote that the number of children produced by an individual is known, and, also, that it is known whether or not he had the affection being considered. T_r and t_r are simply the proportions of children about whom the required information is available.

Let S_r = the number of detected affected people in the secondary generation who come from *sporadic* sibships of size r.

Let $\bar{S}_r$ = the number of detected unaffected people in the secondary generation who come from *sporadic* sibships of size r.

Let s_r = the number of detected affected people in the secondary generation who come from *familial* sibships of size r.

Let $\bar{s}_r$ = the number of detected unaffected people who come from *familial* sibships of size r.

Let A_r = the number of children who come from detected affected sporadics of the secondary generation who in turn come from sibships of size r.

Let $\bar{A}_r$ = the number of children who come from detected unaffected sporadics in the secondary generation who in turn come from sibships of size r.

Let a_r = the number of children who come from detected affected familials in the secondary generation, who in turn come from sibships of size r.

Let P_r = the proportion of affected among all detected children in *sporadic* sibships of size r.

Let p_r = the proportion of affected among all detected children in *familial* sibships of size r.

Let L = the proportion of all detected affected propositi in the secondary generation from sibships of size two or greater who are familials.

It is to be noted that all these symbols are based only upon sibships which contain a propositus.

To conserve symbols, the bar notation has been borrowed from symbolic logic to mean the "negative" or opposite of. It is not intended, as it has been used here, to designate a mean, which is its more usual use in statistics.

We shall use the symbol "$\mathbf{E}\rightarrow$" to stand for the third person singular of the verb "to estimate."

Henceforth, we shall use the verb "to estimate" and the symbol "$\mathbf{E}\rightarrow$" in a special sense. If χ is a number and C is a statistic, we shall say C estimates χ [$C\ \mathbf{E}\rightarrow \chi$], if, as our information about χ becomes infinite, C converges in probability to χ. Note that the word and symbol do *not* imply unbiased estimates. Some of the estimates to be derived here will in fact be biased, but the bias will in every case be of a lower order of magnitude than the standard error, and therefore of no serious consequence. Expressions for removing the bias will, however, be included. We shall adopt the convention that wherever the summation sign is used, it pertains to the variable r and goes from 2 to infinity, or to the number which equals the largest sibship size in the sample.

Now let us suppose finally that our sample consists of a total of n sibships in the secondary generation.

On the assumption of single ascertainment, it can be shown (Weinberg, 1913; Greenwood and Yule, 1914) that

$$B_r\ \mathbf{E}\rightarrow \frac{r\theta_r}{\sum r\theta_r}$$

and

$$b_r\ \mathbf{E}\rightarrow \frac{r\psi_r}{\sum r\psi_r}.$$

In point of fact, the above statements do require other assumptions in addition to the one of single ascertainment. They will be briefly discussed in the paragraph on special assumptions.

1. The partial mean fertility of affected

$$A_r \mathbf{E}\!\rightarrow (1 - L)nrB_rT_rP_r\hat{\Omega}_r ,$$

and, moreover,

$$B_r \mathbf{E}\!\rightarrow \frac{r\theta_r}{\sum r\theta_r}, \quad \text{and} \quad P_r = \frac{S_r}{(1 - L)n\,rB_rT_r}$$

so that

$$\frac{A_r}{S_r} B_r \mathbf{E}\!\rightarrow \frac{r\theta_r\hat{\Omega}_r}{\sum r\theta_r}.$$

$$a_r \mathbf{E}\!\rightarrow Lnrb_rt_rp_r\omega_r ,$$

and

$$b_r \mathbf{E}\!\rightarrow \frac{r\psi_r}{\sum r\psi_r} \quad \text{and} \quad p_r = \frac{s_r}{Lnrb_r\,t_r}$$

so that

$$\frac{a_r}{s_r} b_r \mathbf{E}\!\rightarrow \frac{r\psi_r\,\omega_r}{\sum r\psi_r}.$$

Thus,

$$(1 - \lambda) \sum \frac{A_r}{S_r} B_r + \lambda \sum \frac{a_r}{s_r} b_r \mathbf{E}\!\rightarrow \omega',$$

or, taking L to be an estimate of λ, we have

$$\boxed{(1 - L) \sum \frac{A_r}{S_r} B_r + L \sum \frac{a_r}{s_r} b_r \mathbf{E}\!\rightarrow \omega'} .$$

2. The partial mean fertility of unaffected

$$\bar{A}_r \mathbf{E}\!\rightarrow (1 - L)nrB_r(1 - P_r)T_r\Omega_r ,$$

but again,

$$B_r \mathbf{E}\!\rightarrow \frac{r\theta_r}{\sum r\theta_r} \quad \text{and} \quad 1 - P_r = \frac{\bar{S}_r}{(1 - L)n\,rB_r\,T_r},$$

so that

$$\frac{\bar{A}}{\bar{S}_r} B_r \mathbf{E}\!\rightarrow \frac{r\theta_r\Omega_r}{\sum r\theta_r}, \quad \text{and}$$

$$\boxed{\sum \frac{\bar{A}_r}{\bar{S}_r} B_r \longmapsto \Omega'} .*$$

3. *The partial fitness*

Now let w' be the estimate of ω', and let W' be the estimate of Ω' as obtained above. Then our estimate of the fitness of affected becomes

$$\frac{w'}{W'}.$$

C. *The fertility and fitness of married people*

1. *General considerations*

Dr. W. J. Schull has pointed out to me that in the case of affections involving a conspicuous cosmetic disability it may be of interest to inquire to what extent any observed reduction in fitness is due to the low proportion of affected who marry. There are a number of questions which one might ask of the data in this connection. Two of them are:

1) Is the proportion of affected persons who marry significantly less than the proportion of unaffected persons who marry?

2) Is the fertility of affected persons who marry substantially the same as the fertility of married people in the general population?

If the answer to both questions is yes, then it may perhaps be argued that the failure of affected to marry is primarily responsible for their low fitness and that the selective pressure against the gene or trait may indeed be largely due to cosmetic factors.

We shall here consider a method for answering the second question, using sib controls, though we shall have, as before, to confine ourselves to *partial* fertilities.

We shall make all the assumptions we have made in the preceding discussion and the arguments to be developed will be closely analogous. We are, of course, still considering a dominant-type condition.

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* The reader's attention is called to the possibility that $\frac{\bar{A}_r}{\bar{S}_r}$ may not exist for values of r for which B_r is not zero. This possibility will always be realized, when ascertainment is through affected individuals, in the case of $r = 1$, for there will be no unaffected children in the sample from sibships of size one. This is the reason that partial mean fertility, rather than mean fertility, has to be estimated.

The possibility that $\frac{\bar{A}_r}{\bar{S}_r} Br$ may not exist for $r > 1$, is more of a theoretical difficulty than a practical one. For small values of r (other than one) there are almost certainly going to be enough sibships so that, even in the case when the proportion of all unaffected sporadics who are detected is quite small, $\bar{S}_r$ will not equal zero, while for large values of r, B_r is apt to be sufficiently small that $\frac{\bar{A}_r}{\bar{S}_r} B_r$, even when it does exist, does not contribute much. Moreover, for large values of r, there will almost always be at least one detected unaffected sporadic in each sibship. The practical problem, therefore, is really limited to sibships of one, and these have got to be eliminated.

2. Expressions for fertility and fitness in the population

We shall employ all the symbols used previously, but we shall note by the subscript m in parentheses, (m), when they apply only to *married* persons of a particular type. *Unless the subscript (m) is present*, the symbol refers to precisely the same quantity that it did in the previous section.

We shall in addition require several new symbols for this paragraph:

Let Γ_r = the proportion of people, among all those unaffected people in the population who come from sibships of size r produced by normal x normal matings, who are married.

Let $\hat{\Gamma}_r$ = the proportion of people, among all those affected people in the population who come from sibships of size r produced by normal x normal matings, who are married.

Let γ_r = the proportion of people, among all those affected people in the population who come from sibships of size r produced by affected x normal matings, who are married.

Let $\hat{\gamma}_r$ = the proportion of married people, among all those unaffected people in the population who come from sibships of size r produced by affected x normal matings, who are married.

Now if $\Omega'_{(m)}$ is the partial mean fertility of married persons, then we may write

$$\Omega'_{(m)} = \frac{\begin{array}{r}(1-\pi)](1-\rho_1)\sum r\theta_r\Gamma_r\Omega_{r(m)} + \rho_1\sum r\theta_r\hat{\Gamma}_r\hat{\Omega}_{r(m)}] \\ + \pi[\rho_2\sum r\psi_r\gamma_r\omega_{r(m)} + (1-\rho_2)\sum r\psi_r\hat{\gamma}_r\hat{\omega}_{r(m)}]\end{array}}{\begin{array}{r}(1-\pi)[(1-\rho_1)\sum r\theta_r\Gamma_r + \rho_1\sum r\theta_r\hat{\Gamma}_r] \\ + \pi[\rho_2\sum r\psi_r\gamma_r + (1-\rho_2)\sum r\psi_r\hat{\gamma}_r]\end{array}}$$

(1) where, as before, the summations are from r = 2 to r = ∞, and

(2) where the (m) subscript is used in the sense described above. (Thus, for example, $\Omega_{r(m)}$ is the average fertility of unaffected *married* people who come from sibships of size r produced by normal x normal matings, and, similarly, for the other omegas.)

As before, we may simplify by assuming ρ_1 and π are each small compared with one so that

$$\Omega'_{(m)} = \frac{\sum r\theta_r\Gamma_r\Omega_{r(m)}}{\sum r\theta_r\Gamma_r}$$

For the PMF of affected married persons, $\omega'_{(m)}$, we may write

$$\omega'_{(m)} = \frac{(1-\pi)\rho_1\sum r\theta_r\hat{\Gamma}_r\hat{\Omega}_{r(m)} + \pi\rho_2\sum r\psi_r\gamma_r\omega_{r(m)}}{(1-\pi)\rho_1\sum r\theta_r\hat{\Gamma}_r + \pi\rho_2\sum r\psi_r\gamma_r},$$

or

$$\omega'_{(m)} = [1-\lambda_{(m)}]\frac{\sum r\theta_r\hat{\Gamma}_r\hat{\Omega}_{r(m)}}{\sum r\theta_r\hat{\Gamma}_r} + \lambda_{(m)}\frac{\sum r\psi_r\gamma_r\omega_{r(m)}}{\sum r\psi_r\gamma_r}$$

where

$$\lambda_{(m)} = \frac{\pi\rho_2 \sum r\psi_r\gamma_r}{(1-\pi)\rho_1 \sum r\theta_r\hat{\Gamma}_r + \pi\rho_2 \sum r\psi_r\gamma_r}$$

that is, the proportion of familials among all affected married persons.

3. Expressions for fertility and fitness in the sample

We shall use the m subscript as above*, but, in addition, we shall need the following symbols:

Let F_r = the number of *married* detected affected sporadics in the secondary generation, who come from sibships of size r.

Let $\bar{F}_r$ = the number of *married* detected unaffected sporadics in the secondary generation, who come from sibships of size r.

Let f_r = the number of married detected familials in the secondary generation, who come from sibships of size r.

These three symbols, again, are based only on sibships which contain a propositus. Then

$$F_r \mathbf{E}\rightarrow (1-L)nrB_rP_rT_r\hat{\Gamma}_r$$

but

$$B_r \mathbf{E}\rightarrow \frac{r\theta_r}{\sum r\theta_r} \quad \text{and} \quad P_r = \frac{S_r}{(1-L)nrB_rT_r},$$

hence

$$\frac{F_r}{S_r} Br \mathbf{E}\rightarrow \frac{r\theta_r\hat{\Gamma}_r}{\sum r\theta_r}.$$

Moreover, $A_{r(m)} \mathbf{E}\rightarrow F_r\Omega_{r(m)}$, so that

$$\frac{\sum \frac{A_{r(m)}}{S_r} B_r}{\sum \frac{F_r}{S_r} B_r} \mathbf{E}\rightarrow \frac{\sum r\theta_r\hat{\Gamma}_r\hat{\Omega}_{r(m)}}{\sum r\theta_r\hat{\Gamma}_r}.$$

Now, $f_r \mathbf{E}\rightarrow Lnrb_rt_rp_r\gamma_r$
and again

$$b_r \mathbf{E}\rightarrow \frac{r\psi_r}{\sum r\psi_r}, \quad a_{r(m)} \mathbf{E}\rightarrow f_r\,\omega_{r(m)}, \quad \text{and} \quad p_r = \frac{s_r}{Lnrb_r\,t_r},$$

so that, much as before

* Thus $A_{r(m)}$, $a_{r(m)}$, and $\bar{A}_{r(m)}$ will refer to the number of children of married people.

$$\frac{\sum \frac{a_{r(m)}}{s_r} b_r}{\sum \frac{f_r}{s_r} b_r} \mathbf{E}\rightarrow \frac{\sum r\psi_r \gamma_r \omega_{r(m)}}{\sum r\psi_r \gamma_r}.$$

If we estimate $\lambda_{(m)}$ by $L_{(m)}$, the observed proportion of detected affected married propositi from sibships of size two or greater who are familials, we may write

$$[1 - L_{(m)}] \frac{\sum \frac{A_{r(m)}}{S_r} B_r}{\sum \frac{F_r}{S_r} B_r} + L_{(m)} \frac{\sum \frac{a_{r(m)}}{s_r} b_r}{\sum \frac{f_r}{s_r} b_r} \mathbf{E}\rightarrow \omega'_{(m)}.$$

Note incidentally that the quantities S_r, s_r, b_r, and B_r are the same quantities used in preceding sections. *They* do not refer only to the sample of married persons.

Now consider the estimate of the mean partial fertility of all married persons.

$$\bar{F}_r \mathbf{E}\rightarrow (1 - L)nrB_rT_r(1 - P_r)\Gamma_r.$$

$$_r B\mathbf{E}\rightarrow \frac{r\theta_r}{\sum r\theta_r}, \quad 1 - P_r = \frac{\bar{S}_r}{(1 - L)nrB_r T_r}, \quad \text{and} \quad \bar{F}_r \Omega_{r(m)} \mathbf{E}\rightarrow \bar{A}_{r(m)},$$

so that

$$\frac{\sum \frac{\bar{A}_{r(m)}}{\bar{S}_r} B_r}{\sum \frac{\bar{F}_r}{\bar{S}_r} B_r} \mathbf{E}\rightarrow \Omega'_{(m)}$$

If $W'_{(m)}$ is our estimate of $\Omega'_{(m)}$ and $w'_{(m)}$ is our estimate of $\omega'_{(m)}$, then $\frac{w'_m}{W'_m}$ will provide an estimate of the partial fitness.

GENERALITY OF THE METHOD FOR A RARE DOMINANT TRAIT

The methods which were presented above for a rare dominant trait may be used for any rare affection where the people in the secondary generation can be classified according to whether they have or have not an affected parent and where affected children from unaffected by unaffected matings rarely, if ever, occur more than once in a sibship. It is not necessary that the "sporadic" persons be mutants. They may owe their affection to some covert genetic attribute of their parents. Whether one would care to make the assumptions which have been necessary to derive the method (and which will be set out in more detail subsequently) in such circumstances is another matter. However, algebraically, the method is the same.

The formulae which have been presented here may also be used to compute partial mean fertility and partial mean fitness for the sexes separately. If we divide the sample into a subsample of males and a subsample of females, and if we use the subscript M to denote numbers computed solely on the basis of males, then we may write

$$(1 - L_M) \sum \frac{A_{rM}}{S_{rM}} B_r + L_M \sum \frac{a_{rM}}{s_{rM}} b_r \mathrel{\mathbf{E}\!\!\rightarrow} \omega'_M$$

where L_M, for example, is the proportion of all male propositi in the secondary generation from sibships greater than two who are familials. A_{rM} or a_{rM} refer to the number of children of males. Moreover,

$$\sum \frac{\bar{A}_{rM}}{\bar{S}_{rM}} B_r \mathrel{\mathbf{E}\!\!\rightarrow} \Omega'_{(M)},$$

and, again for the fitness of married persons,

$$[1 - L_{(m)M}] \frac{\sum \frac{A_{r(m)M}}{S_{rM}} B_r}{\sum \frac{F_{rM}}{S_{rM}} B_r} + L_{(m)M} \frac{\sum \frac{a_{r(m)M}}{s_{rM}} b_r}{\sum \frac{f_{rM}}{s_{rM}} b_r} \mathrel{\mathbf{E}\!\!\rightarrow} \omega'_M$$

and

$$\frac{\sum \frac{\bar{A}_{r(m)M}}{\bar{S}_{rM}} B_r}{\sum \frac{\bar{F}_{rM}}{\bar{S}_{rM}}} \mathrel{\mathbf{E}\!\!\rightarrow} W_M$$

One of course uses exactly analogous formulae for females.

It should be pointed out that the only additional assumption required here is that in the population the sex-ratio among the children of affected and unaffected is not influenced by family size.

A RARE RECESSIVE CONDITION

The use of sibs as controls in the case of a recessive trait is at best a dubious procedure since, we we shall see in the paragraph on special assumptions, it is necessary to assume that the fertility of carriers, who are genetically a special group, is the same as the fertility of people in the general population, which may well be untrue.

Algebraically, however, the estimates of fertility can be obtained just as before. If we use capital letters to designate numbers pertaining to unaffected and small letters to designate those pertaining to affected, we have

$$\sum \frac{a_r}{s_r} b_r \mathrel{\mathbf{E}\!\!\rightarrow} \omega'$$

and

$$\sum \frac{A_r}{S_r} b_r \mathrel{\mathbf{E}\!\!\rightarrow} \Omega',$$

b_r being the distribution of sibship sizes in the whole sample.

These estimators can almost immediately be transformed by analogy with the

previous ones, to obtain individual estimates of fertility for the two sexes, and also for married people.

CONDITIONS OF SAMPLING

Exhaustive ascertainment

We may now go on to consider the case of exhaustive ascertainment. This type of ascertainment prevails when we detect all sibships, from a particular kind or kinds of mating, which produce at least one affected.

We again consider that we have some information about three generations, and that the propositi occur in the secondary generation. The estimates of fitness are assumed to be based only on sibs in exhaustively ascertained sibships.

The expressions for fertility and fitness in the population need not be derived again since, of course, they do not depend upon how we ascertain our data.

ESTIMATORS FOR THE CASE OF EXHAUSTIVE ASCERTAINMENT

A. Estimators for a rare dominant trait using the method analogous to that used for single ascertainment

Let us first consider the same approach we used for single ascertainment. Our previous estimators follow from the solution of two problems of estimation: the estimation of the omegas—the population sibship-size specific fertilities, and the estimation of $\frac{r\theta_r}{\sum r\theta_r}$ or $\frac{r\psi_r}{\sum r\psi_r}$, the factor appropriate for weighting each of the fertilities. The reader may easily verify that in exhaustive ascertainment the omegas can be estimated in the same manner as in single ascertainment. The quantities estimated by B_r and b_r are different, however.

Consider the case of a rare dominant trait. We find

$$B_r \mathrel{\mathbf{E}}\!\!\rightarrow \frac{[1-(1-\rho_1)^r]\theta_r}{\sum [1-(1-\rho_1)^r]\theta_r}$$

(Weinberg, 1913; Greenwood & Yule, 1914), and

$$b_r \mathrel{\mathbf{E}}\!\!\rightarrow \frac{[1-(1-\rho_2)^r]\psi_r}{\sum [1-(1-\rho_2)^r]\psi_r}$$

Now let $W_r = \frac{\bar{A}_r}{S_r}$, i.e. $W_r \mathrel{\mathbf{E}}\!\!\rightarrow \Omega_r$; $\hat{W}_r = \frac{A_r}{S_r}$, i.e. $W_r \mathrel{\mathbf{E}}\!\!\rightarrow \hat{\Omega}_r$; and $w_r = \frac{a_r}{s_r}$, i.e. $w_r \mathrel{\mathbf{E}}\!\!\rightarrow \omega_r$. The "estimation-identities" on the extreme right can be demonstrated by the methods given in previous sections. Then

$$W = \frac{\sum \frac{B_r}{1-(1-\rho_1)^r} W_r}{\sum \frac{B_r}{1-(1-\rho_1)^r}} \mathrel{\mathbf{E}}\!\!\rightarrow \Omega'$$

$$w' = (1 - \ell)\frac{\sum \frac{B_r}{1 - (1 - \rho_1)^r}\hat{W}_r}{\sum \frac{B_r}{1 - (1 - \rho_1)^r}} + \ell\frac{\sum \frac{b_r}{1 - (1 - \rho_2)^r}w_r}{\sum \frac{b_r}{1 - (1 - \rho_2)^r}} \mathrel{E}\!\!\rightarrow \omega'$$

where, as before, the summations are from r = 2, and where ℓ is the proportion of *all* affected from exhaustively ascertained sibships of size two or greater who are familials.

Now we have, earlier, assumed that ρ_1 is small compared with one, and it would be possible to show (Weinberg, 1913; Krooth, 1952b) that under this assumption the expressions for W′ and for the estimate of the PMF of affected sporadics reduces to the same quantities which were employed in the case of single ascertainment. However, the estimator for the PMF of affected familials is unique, and rather intractable. Also, one might inquire whether the more elaborate sampling employed in exhaustive ascertainment could not be used to obtain estimators with smaller variances.

B. Special estimators for exhaustive ascertainment

Another approach has been employed which, in the author's view, yields more desirable estimators. This method really involves nothing more than taking the estimators just derived one step further.

Let X_r = the proportion of all affected sporadics in the sample (in the secondary generation) who come from sibships of size r.

Let x_r = the proportion of all affected familials in the sample (in the secondary generation) who come from sibships of size r.

We shall use all the other symbols in the same sense as before. Now

$$P_r \mathrel{E}\!\!\rightarrow \frac{\rho_1}{[1 - (1 - \rho_1)^r]}$$

and

$$p_r \mathrel{E}\!\!\rightarrow \frac{\rho_2}{[1 - (1 - \rho_2)^r]}.$$

now

$$x_r = \frac{Lnrb_r p_r}{Ln \sum rb_r p_r},$$

but

$$rb_r p_r \mathrel{E}\!\!\rightarrow \frac{\rho_2 r\psi_r}{\sum (1 - \rho_2)^r\psi_r},$$

so that

$$x_r \mathrel{E}\!\!\rightarrow \frac{r\psi_r}{\sum r\psi_r},$$

and by similar reasoning

$$x_r \mathbf{E}\rightarrow \frac{r\theta_r}{\sum r\theta_r}.$$

1. A rare dominant trait

Thus, in exhaustive ascertainment, we may write, for a rare dominant condition,

$$\sum W_r X_r \mathbf{E}\rightarrow \Omega'$$

and

$$(1-\ell)\sum \hat{W}_r X_r + 1\sum w_r x_r \mathbf{E}\rightarrow \omega',$$

where, as always, the summations begin at r = 2 and where, again, ℓ is the proportion of all affected in the secondary generation from sibships of size two or greater, who are familials. (Since ascertainment is exhaustive, we include *all* the affected in the exhaustively ascertained sibships.)

In single ascertainment, it will be remembered, each ascertained sibship had only one propositus who was counted in determining the value of ℓ or L. Now all the persons in ascertained sibships may be used.

Now let us obtain estimates for the fertility of married affected.

Let g_r = the proportion of affected, in sample sibships of size r in the secondary generation, who are married, so that $g_r \mathbf{E}\rightarrow \gamma_r$.

Let $x_{r(m)}$ = the proportion of married affected who come from sibships of size r. (We shall continue to use the subscript m in the same sense as before.) Now

$$x_{r(m)} = \frac{rB_r\, p_r\, g_r}{\sum rB_r\, g_r} \mathbf{E}\rightarrow \frac{r\theta_r\, \gamma_r}{\sum r\theta_r\, \gamma_r},$$

which follows by simple substitution from the previous estimation-identities.

Hence,

$$W = \sum W_{r(m)} X_{r(m)} \mathbf{E}\rightarrow \Omega'_{(m)}$$

and

$$w = (1-\ell_{(m)})\sum \hat{W}_{r(m)} X_{r(m)} + \ell_{(m)} \sum w_{r(m)} x_{r(m)} \mathbf{E}\rightarrow \omega'_{(m)}.$$

In every case, as before, the formulae may be broken down into separate estimates for males and females simply by basing the W's and the ℓ-value only on either the males or females respectively.

2. A rare recessive trait

For a recessive trait, the formulae are

$$W = \sum W_r X_r \mathbf{E}\rightarrow \Omega,$$

and

$$w = \sum w_r x_r \longmapsto \omega,$$

and further subdivisions of these fertilities are again immediately derivable.

C. *Properties of the special estimators for exhaustive ascertainment*

It may be noted that in exhaustive ascertainment fitness of course is again estimated by w/W in each case.

The chief relations between the estimators in single and exhaustive ascertainment may be summarized thus:

(1) In exhaustive ascertainment ℓ replaces L as the weighting factor appropriate for combining the fertilities of affected and sporadic cases. Since ℓ is based on more individuals than L, it will, other things being equal, have a smaller variance.

(2) In exhaustive ascertainment X_r and x_r replace B_r and b_r as the weighting factors appropriate for combining the individual sibship-size-specific means. $X_r = B_r$, so that for sporadic cases the difference is purely one of notation.* For familial cases, however, x_r will be based on larger numbers than b_r and will, other things being equal, have a smaller variance.

(3) It is assumed that all sibs within the sibship are ascertained.

(4) The reader's attention is called to the fact that we are here considering only the two "classical kinds of ascertainment: single and exhaustive. There of course exists an intermediate case.† In this connection, it is instructive to note that in the estimators for single ascertainment, the factors appropriate for weighting W_r and w_r are, respectively, B_r and b_r—which correspond, in single ascertainment, where there is but one propositus per sibship, to the proportion of propositi who come from sibships of size r. When there is exhaustive ascertainment, we weight by X_r and x_r which again correspond to the proportion of propositi who come from sibships of size r, since now in a sense *all* affected are propositi.

VARIANCES AND BIASES

The derivations here will be outlined only briefly. The computing formulae are given in section XI.

All the estimators presented in this paper can be reduced to certain standard forms.

A. *Expressions for variances and covariances in cases other than the one of married individuals under single ascertainment*

1. *Variances of statistics of the form* $\sum W_r B_r$

If W_r is a sibship-size-specific mean and if B_r is a multionomial proportion, then the variance $\sum W_r B_r$ can be shown to be:

* It was remarked earlier, using the other approach, that for sporadic cases and their sibs the estimates of fertility under the two systems of ascertainment are the same. The reader may verify that this is also true using the "special" approach.

† Exhaustive and single ascertainment, and the intermediate case, by no means cover all possible kinds of ascertainment, however.

$$\operatorname{var}(\sum W_r B_r) = \mathcal{E}(\sum W_r B_r)^2 - (\mathcal{E}\sum W_r B_r)^2 = \mathcal{E}(\sum \delta_{\Omega_r} \mathcal{E} B_r)^2 + \mathcal{E}(\sum \delta_{B_r} \Omega_r)^2 + \mathcal{E}(\sum \delta_{B_r} \delta_{\Omega_r})^2,$$

where

$$W_r \mathrel{E}\!\!\rightarrow \Omega_r \quad \text{and} \quad \delta_{\Omega_r} = W_r - \Omega_r,$$

$$B_r \mathrel{E}\!\!\rightarrow \mathcal{E}B_r \quad \text{and} \quad \delta_{B_r} = B_r - \mathcal{E}B_r,$$

from which, using the identity

$$\mathcal{E}(\sum x_i)^2 = \sum \mathcal{E}x_i^2 + \sum_{i \neq j} \mathcal{E}x_i x_j,$$

and using also the multinomial expressions for the variance of B_r and the covariance of B_r and B_s to obtain $\mathcal{E}\delta_{B_r}^2$ and $\mathcal{E}\delta_{B_r}\delta_{B_s}$, the computing formulae for variance of $\sum W_r B_r$ can be obtained.

If Z_r is the variance of W_r and if B_r is based on $(1 - L)n$ individuals, then the variance of $\sum W_r B_r$ is

$$\sum B_r^2 Z_r + \frac{\sum B_r (W_r - W)^2 + \sum B_r (Z_r - B_r Z_r)}{(1 - L)n}$$

where $W = \sum B_r W_r$.

2. A linear combination of two statistics of the form $\sum \hat{W}_r B_r$

If we have $w' = (1 - L)\sum \hat{W}_r B_r + L \sum \hat{w}_r b_r$,

where $\hat{W}_r$ and $\hat{w}_r$ are independent sibship-size-specific means,

where b_r is another independent multinomial probability and where L is a binomial proportion based on fairly large numbers, then

$$\operatorname{var} w = (1 - L)^2 \operatorname{var}(\sum \hat{W}_r B_r) + L^2 \operatorname{var}(\sum \hat{w}_r b_r) + \left(\frac{\delta w'}{\delta L}\right)^2 \operatorname{var} L.$$

3. The covariance between two statistics of the form $\sum W_r B_r$ and $\sum \hat{W}_r B_r$ *respectively*

$$\operatorname{Cov}(\sum W_r B_r)(\sum \hat{W}_r B_r) = \mathcal{E}(\sum W_r B_r \sum \hat{W}_r B_r) - \mathcal{E}\sum W_r B_r \, \mathcal{E}\sum \hat{W}_r B_r,$$

where $\hat{W}_r$ and W_r are independent sibship-size-specific means, and where the remaining symbols are used as before.

Let $\hat{W}_r \mathrel{E}\!\!\rightarrow \hat{\Omega}_r$.

Then

$$\mathcal{E}(\sum W_r B_r \sum \hat{W}_r B_r) = \mathcal{E}(\sum \Omega_r \mathcal{E} B_r + \sum \delta_{\Omega_r} \mathcal{E} B_r + \sum \delta_{\Omega_r} \delta_{B_r} + \sum \Omega_r \delta_{B_r})(\sum \hat{\Omega}_r \mathcal{E} B_r + \sum \delta_{\hat{\Omega}_r} \mathcal{E} B_r + \sum \delta_{\hat{\Omega}_r} \delta_{B_r} + \sum \hat{\Omega}_r \delta_{B_r})$$

from which we find

$$\operatorname{cov}(\sum W_r B_r \sum \hat{W}_r B_r) = \mathcal{E}\sum \Omega_r \delta_{B_r} \sum \hat{\Omega}_r \delta_{B^r},$$

and from which, in turn, by making use of the identity

$$\mathcal{E} \sum a_i x_i \sum b_i x_i = \sum \mathcal{E} a_i b_i x_i^2 + \sum_{i \neq j} \mathcal{E}(a_i b_j + b_i a_j) x_i x_j$$

and by substituting the multinomial expressions for the variance and covariance of B_r, we obtain

$$\operatorname{cov}\left(\sum W_r B_r \sum \hat{W}_r B_r\right) = \frac{\sum W_r B_r (\hat{W}_r - W)}{(1 - L)n},$$

where $W = \sum W_r B_r$ and where $(1 - L)n$ is the total number the multinomial proportion B_r is based on.

4. Generality of the argument

The same argument holds of course when we are considering X_r, ℓ, and N, etc., rather than B_r, L, and n.

B. Expressions for variances, covariances, and biases in the case of married persons when there is single ascertainment

1. Variance and bias of an expression of the form $\dfrac{\sum W_{r(m)} Q_r B_r}{\sum Q_r B_r}$

$W_{r(m)}$ and B_r are used as before, the former being a sibship-size-specific mean, the latter a multinomial proportion. Q_r (corresponding to the proportion of married persons among all persons of a particular type in sibships of size r) is a binomial proportion, independent of B_r.

Generally, if we have a ratio of the form $\dfrac{u_1}{u_2}$, and if we estimate the numerator by $\hat{u}_1 = u_1 + \epsilon_1$, and the denominator by $\hat{u}_2 = u_2 + \epsilon_2$, we may write*

$$\frac{\hat{u}_1}{\hat{u}_2} = \frac{u_1 + \epsilon_1}{u_2 + \epsilon_2} \mathrel{\mathbf{E}\!\!\rightarrow} \frac{u_1}{u_2}.$$

$$\mathcal{E} \frac{u_1 + \epsilon_1}{u_2 + \epsilon_2} = \mathcal{E} \frac{(u_1 + \epsilon_1)}{u_2\left(1 + \dfrac{\epsilon_2}{u_2}\right)} = \mathcal{E} \frac{u_1 + \epsilon_1}{u_2}\left[1 - \frac{\epsilon_2}{u_2} + \frac{\epsilon_2^2}{u_2^2} + 0(\epsilon_2^3)\right].$$

We shall now assume

(1) Any term in powers of ϵ_1 or ϵ_2 higher than the second is negligible compared with terms in ϵ_1 or ϵ_2 of lower order.

(2) Any term in $\epsilon_1\epsilon_2$ in which the sum of powers of ϵ_1 and ϵ_2 exceeds 2 is negligible compared with terms in $\epsilon_1\epsilon_2$ in which the sum of powers of ϵ_1 and ϵ_2 is less than or equal to 2.

We then find that

$$\mathcal{E} \frac{u_1 + \epsilon_1}{u_2 + \epsilon_2} = \frac{u_1}{u_2} + \left(\frac{u_1}{u_2}\right)^+ \frac{\mathcal{E}\epsilon_2^2}{u_2^2} - \frac{\mathcal{E}\epsilon_1 \epsilon_2}{u_2^2}$$

* $\mathcal{E}\epsilon_1 = \mathcal{E}\epsilon_2 = 0$.

so that the bias,

$$\mathcal{E}\frac{u_1+\epsilon_1}{u_2+\epsilon_2}-\frac{u_1}{u_2}$$

is, approximately,

$$\left(\frac{u_1}{u_2}\right)\frac{\mathcal{E}\epsilon_2^2}{u_2^2}-\frac{\mathcal{E}\epsilon_1\epsilon_2}{u_2^2},$$

while the variance of $\frac{\hat{u}_1}{\hat{u}_2}$ is

$$\operatorname{var}\left(\frac{\hat{u}_1}{\hat{u}_2}\right)=\mathcal{E}\left(\frac{\hat{u}_1}{\hat{u}_2}\right)^2-\left(\mathcal{E}\frac{\hat{u}_1}{\hat{u}_2}\right)^2=\mathcal{E}\frac{\left[\frac{u_1}{u_2}\epsilon_2-\epsilon_1\right]^2}{u_2^2}.$$

We thus have expressions for the bias and variance of $\frac{\hat{u}_1}{\hat{u}_2}$ in terms of u_1, u_2, $\mathcal{E}\epsilon_1^2$, $\mathcal{E}\epsilon_1\epsilon_2$, and $\mathcal{E}\epsilon_2^2$. We may estimate u_1 and u_2 by $\hat{u}_1$ and $\hat{u}_2$ in the variance expression itself. If $u_1=\sum Q_rB_rW_r$ and $u_2=\sum Q_rB_r$ we can find the variance ($\mathcal{E}\epsilon_1^2$ and $\mathcal{E}\epsilon_2^2$) and the covariance, $\mathcal{E}\epsilon_1\epsilon_2$, of numerator and denominator by the ordinary methods (similar to those used in part 1 of this section), using the multinomial and binomial expressions for the variance and covariance when working with B_r and Q_r and by defining Z_r as the variance of W_r.

2. A linear combination of two statistics of the form $\dfrac{\sum W_{r(m)}\,Q_r\,B_r}{\sum Q_r\,B_r}$

If we have $w'_{(m)}=\dfrac{(1-L)\sum \hat{W}_{r(m)}\,\hat{Q}_r\,B_r}{\sum \hat{Q}_r\,B_r}+\dfrac{L\sum \hat{w}_{r(m)}\,q_r\,b_r}{\sum q_r\,b_r}$, then, exactly as before

$$\operatorname{var} w'_{(m)}=(1-L)^2\operatorname{var}\frac{\sum \hat{W}_{r(m)}\,Q_r\,B_r}{\sum \hat{Q}_r\,B_r}+L^2\operatorname{var}\frac{\sum \hat{w}_r\,q_r\,b_r}{\sum q_r\,b_r}+\left(\frac{\delta w}{\delta L}\right)^2\operatorname{var} L,$$

L again being a binomial proportion.

3. The covariances between two statistics of the form $\dfrac{\sum W_{r(m)}\,Q_r\,B_r}{\sum Q_r\,B_r}$ *and* $\dfrac{\sum \hat{W}_{r(m)}\,\hat{Q}_r\,B_r}{\sum \hat{Q}_r\,B_r}$ *respectively*

Generally, if we have two ratios of the form $\frac{U_1}{U_2}$ and $\frac{u_1}{u_3}$ and if we estimate the parameters thus

$$\hat{U}_1 \mathbf{E}\!\rightarrow U_1 \,;\, \hat{U}_1 - U_1 = H_1$$

$$\hat{U}_2 \mathbf{E}\!\rightarrow U_2 \,;\, \hat{U}_2 - U_2 = H_2$$

$$\hat{u}_1 \mathbf{E}\!\rightarrow u_1 \,;\, \hat{u}_1 - u_1 = \eta_1$$

$$\hat{u}_2 \mathbf{E}\!\rightarrow u_2 \,;\, \hat{u}_2 - u_2 = \eta_2 ,$$

we may write

$$\frac{\hat{u}_1}{\hat{u}_2} = \frac{u_1 + \eta_1}{u_2 + \eta_2} \mathbf{E}\!\rightarrow \frac{u_1}{u_2},$$

and

$$\frac{\hat{U}_1}{\hat{U}_2} = \frac{U_1 + H_1}{U_2 + H_2} \mathbf{E}\!\rightarrow \frac{U_1}{U_2}.$$

It can be shown that

$$\varepsilon\left(\frac{\hat{U}_1}{\hat{U}_2}\right)\left(\frac{\hat{u}_1}{\hat{u}_2}\right) - \varepsilon\frac{\hat{U}_1}{\hat{U}_2}\,\varepsilon\frac{\hat{u}_1}{\hat{u}_2} = \varepsilon\frac{(H_1 - UH_2)(\eta_1 - u\eta_2)}{u_2U_2},$$

approximately, where

$$U = \frac{U_1}{U_2} \quad \text{and} \quad u = \frac{u_1}{u_2}.$$

The expected value of the products of the H's and the η's can be obtained by the ordinary methods.

If either $\frac{\hat{u}_1}{\hat{u}_2}$ or $\frac{\hat{U}_1}{\hat{U}_2}$ is multiplied by a statistic independent of the u's and U's, the covariance is simply multiplied by the same statistic.

C. General notes

The variances obtained, and set out in Section XI, are approximate not only because of the algebraic residues which have been dropped in their derivation, but for another, somewhat subtler, reason.

In a sample series of sibships, the probability that any two persons chosen at random will be sibs is greater than the probability that any two persons chosen at random from the general population will be sibs. Hence, insofar as there is a correlation between sibs for fertility, we shall tend to overestimate the variances of our sibship-size-specific means, for the resemblance between individuals with respect to fertility will be greater in our sample than in a sample of the same number of affected or unaffected individuals chosen at random from the population of affected or the general population.

Note that when the estimate of fertility is confined to a single propositus per sibship, as in affected sporadic cases, this bias does not operate. But when we select two

or more cases from each (or many) of the sibships, as we do with unaffected sporadics or affected familials, then the bias does exist.

It is most unlikely, however, that for large samples this source of error in the variances will be anything but negligible. The algebraic approximations are unlikely to result in an error in the approximate variances of much more than the square of the order of magnitude of the true variance.

SOME SPECIAL ASSUMPTIONS AND PROBLEMS

A. Some special assumptions

We shall here list and briefly examine some of the special assumptions required for the methods which have been presented.

Assumption (1): That for each sibship size r, the fertility of the unaffected sibs of affected (sporadics) is the same as that of people in the general population who are from sibships of the same size.

Assumption (2): That the fertility of the parents of affected (sporadics) is the same as that of the parents of people in the general population.

There are four points which should be made concerning these assumptions.

(a) In the case of a recessive condition, assumptions (1) and (2) would apply to the sibs and parents of affected respectively, and not of course to the sibs and parents of sporadics, for mutants will not be distinguishable as a rule.

(b) It is easy to imagine situations in which Assumption (1) might not hold. The assumption would be violated if, for example, the appearance of an affected in the sibship deterred sibs from reproducing.

(c) Assumption (2) could not reasonably be expected to hold if there were *fertility responses to the birth of an abnormal* (Krooth, 1952), that is, if the production of an abnormal tended, in itself, to cause parents to limit their families (*family limitation*) or to attempt to replace abnormal children by normal ones (*family compensation*) (see the suggestion of Race, 1944). It is, however, often possible to test for the presence of fertility responses by examining the distribution of affected in their sibships with respect to order of birth. We shall not concern ourselves with the details here. Generally, if we find, in a large, informative sample, that affected children appear to fall at random in their sibships, then we are probably safe in assuming that fertility responses, if they exist at all, are small.

(d) One can visualize "fortuitous" situations in which we did indeed get a good estimate of the population fertility when one or both of the assumptions did not hold. Clearly, however, one cannot rely upon such situations, and it is probably unprofitable to use the methods presented here unless both of the assumptions can reasonably be expected to hold, at least approximately.

Assumption (3): That the condition is not etiologically dependent upon the influence of order of birth, parental age, or rate of reproduction.

It might be possible to contrive methods in the case of sufficiently rich data so that this assumption would not be necessary for at least some of the variables. The point, however, is that it *is* necessary for the methods derived in this paper.

Assumptions (1), (2), and (3) are required for the estimation of the partial mean

fertility of unaffected. We shall now go on to consider an assumption which is necessary for the estimation of fitness generally by these methods.

Assumption (4): That the relative fitness of affected, based only upon normals and affecteds who come from sibships of size two or greater is not materially different from the relative fitness based on persons who come from sibships of size one or greater.

This assumption would be violated, to take the most extreme case, if, say, affected persons from sibships of size one were highly infertile compared to normals from sibships of size one, and if affected persons from sibships of size two or greater were highly fertile compared to normals, and if, as a result, the distribution of sibship sizes were such as to render the mean fitness less than one, and the PMF more than one. In this case, we should obviously be led to the wrong conclusion. Just what kind of mechanism could bring such a situation about is unclear, and its occurrence is probably uncommon. However, Assumption (4) is rarely, if ever, likely to hold strictly, and our PMF could never be expected to be more than an approximate estimate of the true mean fitness.*

B. Two general problems associated with the estimation of fitness in a human population

We shall here examine two general problems connected with the estimation of fitness, i.e., ones not peculiar to the approach described in this paper. They do not seem to have been set out clearly before, and an understanding of them is often necessary for the proper interpretation of an estimated fitness.

(a) The time coördinate of an estimate of fitness.

In most (though not all) mathematical models of natural selection, it is assumed that the organism being considered reproduces in discrete generations. Wright (1949) has defined the fitness of a genotype, for this case, in terms of the number of offspring contributed by individuals with the genotype in one generation, to the next generation. Such a definition would work well, for example, in the case of an annual plant. A human population, however, is composed of individuals born at many different times, and can rarely be easily partitioned into groups of people forming discrete generations. It is therefore worthwhile to inquire what period of time is covered by an estimate of human fitness. There are at least three different ways in which the problem could be approached.

(a) The "historical" approach

Suppose that we were able to obtain data on all births in the United States in, say, the year 1860. Imagine that there were N people born in this year and n of them were affected. We might wait until all the people in this population had safely passed the reproductive period, and then divide the average number of children per affected

* Some readers may wonder why, since we have obtained an approximate estimate, it was necessary to develop fairly elaborate formulae. Why, for example, was it necessary to take sibship sizes into account? The answer here is that failing to do so would render our estimate not merely approximate, but systematically wrong, tending to underestimate relative fitness in a determinable way. Obviously, the possible existence of sources of error for which we cannot correct should not deter us from taking reasonable care to correct for factors under our control.

person by the average number of children per person in the whole population to obtain our estimate of fitness. Obviously, this approach is highly unsatisfactory, for, quite apart from the practical difficulties, if fitness changes with time, we should always be about 25–50 years behind.

(*b*) *The annual approach*

In this approach we shall consider all the people alive in a particular year, and it need not be a far-distant one, say 1953. Suppose there were N_{1953} people alive on January 1st of this year and n_{1953} of them were affected. Suppose that between January 1, 1953 and January 1, 1954 the N_{1953} people produced A_{1953} and the n_{1953} people a_{1953} children. We might then define the fitness in 1953 as

$$\Omega_{1953} = \frac{a_{1953}/n_{1953}}{A_{1953}/N_{1953}}$$

which has precisely the same genetical significance as the definition of fitness used in the case of discontinuously reproducing populations. Similarly, the fitness over a period of years, say the years 1 to j (measured from some origin year) is

$$\Omega_{1\to j} = \frac{\sum_{i=1}^{i=j} a_i \Big/ \sum_{i=1}^{i=j} n_i}{\sum_{i=1}^{i=j} A_i \Big/ \sum_{i=1}^{i=j} N_i}.$$

The individual year-specific fitnesses have a linearly additive property over time, that is

$$\Omega_{1\to j} = \sum_{i=1}^{i=j} \frac{y_i}{y} Y_i \Omega_i,$$

where Ω_i is the fitness in the year i, where y_i is the incidence of the affection among all people alive on January 1st of the year i, where Y_i is the proportion of all births in the period of time covered by the years 1 through j, which occurred in the year i, and where y is the incidence of the character among all people alive from January 1, 1 through January 1, j.

(*c*) *The "contemporary" approach*

Now it would be difficult to contrive a method for estimating fitness in a human population which was simpler and more empirical than the "annual" method. It is only rarely, however, that we shall be able to obtain the necessary data to allow for estimates of annual fitness. More frequently, we shall be obliged to take a random sample of, say, all living perople (or all people who were alive during a particular interval of time), and then find the average number of children per affected and the average number of children per person in general. This way of examining the problem we shall note as the contemporary approach, and it is the one used in the present paper.

The contemporary approach will clearly reflect the fertility and mortality experience of the population over a considerable period of time. What we are effectively

doing is taking a human population with a specified age distribution, and considering it as a single generation. This, almost certainly, is permissible. It would, however, be desirable to develop exact algebraic identities relating the annual fitnesses to the fitness obtained by the contemporary approach. The solution to this problem seems curiously elusive at the present time. Recently Leslie (1948) has given an elegant formal solution to a closely related problem in the general mathematical theory of populations, and it may be that the result he obtains can be used to clarify the time significance of a contemporary estimate of fitness.

What is important, at present, is that since the contemporary estimate reflects population experience over a considerable period of time, it is not apt to be a very meaningful measure if the fitness has changed markedly over the life span of the people being studied. Thus a contemporary estimate of the fitness of persons with diabetes mellitus made now would be a "hodgepodge" of the fitness before insulin and the fitness afterwards.

(b) The dependence of the required conditions of sampling on the purposes for which an estimate of fitness is computed.

Let us at the outset of this discussion consider *why* we are measuring fitness. There are, of course, many possible reasons, but two may be singled out as being especially important:

(1) Because we wish to obtain an estimate of the selective pressure for or against the genotype in some general population; (2) because we wish to demonstrate the presence or absence of some difference in fertility ascribable solely to genotype.

These two reasons are not equivalent, and the character of the computations and the assumptions depends upon which one the investigator is concerned with.

If we are studying fertility for reason (1), then our conditions of sampling must be such as to ensure that we have a random sample of affected, and a random sample of the general population. We do *not* wish to standardize the mean fertility of affected people for, say, the general population age and social class distributions, if there are differences between the affected and the general population with respect to these attributes. Such differences may form part of the selective mechanism, even when they have nothing to do with the actions of the genes involved.

If we are studying fitness for reason (2), the problem becomes more complicated. The first and most obvious comparison would be between affected individuals and unaffected individuals, rather than between affected and total population. Here, the conditions of sampling require that the affected group be a random sample of all affected, and, analogously, the unaffected group a random sample of all unaffected. However, such a comparison may not be sufficient to allow us to speak of differences "ascribable solely to genotype." Suppose, for example, the genotype under consideration was found mainly in persons who were immigrants from a culture where people did not practice birth control. If the affected individuals had an unusually high fertility, would it be because they were affected or because they were immigrants? Hence, one might wish to standardize for cultural background. On the other hand, it may not always be clear whether some extraneous variables, such as, say, social class, show an unusual distribution among affected for a trivial reason or for a reason which has to do with the action of the gene.

The methods developed in the present paper were designed for the estimation of fitness for reason (1). If the investigator were concerned to study fitness for reason (2), the simplest thing to do (rather than estimate fitness which has a less clear meaning under this alternative) in data which consisted of affected children and their sibs, would be to compare the average number of children per affected with the average number of children per unaffected, *for each sibship size* (and by suitable transformation the individual sibship-size-specific probabilities could be converted to chi-squares and added [Fisher, 1950]). Note that when sibs are used as controls for this purpose, special assumptions (1), (2), and (4) are not necessary. The new, and more general assumption—which really includes special Assumption (3)—is that any fertility difference observed between affected and their sibs is due solely to genotype. In most (though not necessarily all) cases, one would now probably wish to use the sibs of familial cases as controls for the familial affected, and similarly, sibs of sporadics as controls for sporadic affected.

It is suggested that such comparisons of the kind described above may often prove helpful when studying fertility for reason (2). It is not suggested that the results will necessarily be conclusive and free of ambiguity.

From the preceding discussion it is clear that the character of the computations and the assumptions as well as the conditions of sampling which are required, all depend upon the reasons for which one is estimating fitness and fertility.

COMPUTER'S SUMMARY

A. Estimators

The estimators developed in this paper are given in Table 1. The following is intended as a guide to the table:

1. Definitions of symbols

Let w' = our estimate of the PMF of the affected.

Let W' = our estimate of the PMF of general population.

Let B_r = the proportion of all those sibships in the secondary generation, of size two or greater and containing an affected sporadic, which are of size r.

Let b_r = the proportion of all those sibships in the secondary generation, of size two or greater and containing one or more affected familials, which are of size r, *or*, in the case of a recessive, the proportion of all those sibships in the secondary generation, of size two or greater, which are of size r.

Let $\hat{w}_r$ = the average number of children per affected person who comes from a familial sibship (in the secondary generation) of size r, *or*, in the case of a recessive, the average number of children per affected person who comes from a sibship (in the secondary generation) of size r.

Let $\hat{W}_r$ = the average number of children per affected person who comes from a sporadic sibship (in the secondary generation) of size r.

Let W_r = the average number of children per unaffected person who comes from a sporadic sibship (in the secondary generation) of size r, *or*, in the case of a recessive, the average number of children per unaffected person who comes from a sibship (in the secondary generation) of size r.

TABLE 1.—ESTIMATORS

System of Ascertainment	Condition	w′	W′
Single ascertainment	A. Rare dominant		
	1. Total fitness	$(1 - L)\Sigma\hat{W}_r B_r + L\Sigma\hat{w}_r b_r$	$\Sigma W_r B_r$
	a. Fitness of males	$(1 - L_M)\Sigma\hat{W}_{rM} B_r + L_M\Sigma\hat{w}_{rM} b_r$	$\Sigma W_{rM} B_r$
	2. Fitness of married persons	$\frac{(1 - L_{(m)})}{\Sigma\hat{Q}_r B_r}\Sigma\hat{W}_{r(m)}\hat{Q}_r B_r + \frac{L_{(m)}\Sigma}{\Sigma q_r b_r}\hat{w}_{r(m)} q_r b_r$	$\frac{\Sigma W_{r(m)} Q_r B_r}{\Sigma Q_r B_r}$
	a. Fitness of married males	$\frac{(1 - L_{(m)M})}{\Sigma\hat{Q}_{rM} B_r}\Sigma\hat{W}_{r(m)M}\hat{Q}_{rM} B_r + \frac{L_{(m)M}}{\Sigma q_{rM} b_r}\Sigma\hat{w}_{r(m)M} q_{rM} b_r$	$\frac{\Sigma W_{r(m)M} Q_{rM} B_r}{\Sigma Q_{rM} B_r}$
	B. Rare recessive		
	1. Total fitness	$\Sigma\hat{w}_r b_r$	$\Sigma W_r b_r$
	a. Fitness of males	$\Sigma\hat{w}_{rM} b_r$	$\Sigma W_{rM} b_r$
	2. Fitness of married persons	$\frac{\Sigma\hat{w}_{r(m)} q_r b_r}{\Sigma q_r b_r}$	$\frac{\Sigma W_{r(m)} Q_r b_r}{\Sigma Q_r b_r}$
	a. Fitness of married males	$\frac{\Sigma\hat{w}_{r(m)M} q_{rM} b_r}{\Sigma q_{rM} b_r}$	$\frac{\Sigma W_{r(m)M} Q_{rM} b_r}{\Sigma Q_{rM} b_r}$
Exhaustive ascertainment	A. Rare dominant		
	1. Total fitness	$(1 - \ell)\Sigma\hat{W}_r X_r + \ell\Sigma\hat{w}_r x_r$	$\Sigma W_r X_r$
	a. Fitness of males	$(1 - \ell_M)\Sigma\hat{W}_{rM} X_r + \ell_M\Sigma\hat{w}_{rM} x_r$	$\Sigma W_{rM} X_r$
	2. Fitness of married persons	$(1 - \ell_{(m)})\Sigma W_{r(m)} X_{r(m)} + \ell_{(m)}\Sigma\hat{w}_{r(m)} x_{r(m)}$	$\Sigma W_{r(m)} X_{r(m)}$
	a. Fitness of married males	$(1 - \ell_{(m)M})\Sigma W_{r(m)M} X_{r(m)} + \ell_{(m)M}\Sigma\hat{w}_{r(m)M} x_{r(m)}$	$\Sigma W_{r(m)M} X_{r(m)}$
	B. Rare recessive		
	1. Total fitness	$\Sigma\hat{w}_r x_r$	$\Sigma W_r x_r$
	a. Fitness of males	$\Sigma\hat{w}_{rM} x_r$	$\Sigma W_{rM} x_r$
	2. Fitness of married persons	$\Sigma\hat{w}_{r(m)} x_{r(m)}$	$\Sigma W_{r(m)} x_{r(m)}$
	a. Fitness of married males	$\Sigma\hat{w}_{r(m)M} x_{r(m)}$	$\Sigma W_{r(m)M} x_{r(m)}$

Let X_r = the proportion of all affected sporadics in the secondary generation from sibships of size two or greater, who come from sibships of size r.

Let x_r = the proportion of all affected familials in the secondary generation, from sibships of size two or greater, who come from sibships of size r, *or*, in the case of a recessive, the proportion of all affected in the secondary generation, from sibships of size two or greater, who come from sibships of size r.

Let q_r = the proportion of affected familials in the secondary generation, from sibships of size r, who are married, *or*, in the case of a recessive, the proportion of all affected persons in the secondary generation, from sibships of size r, who are married.

Let $\bar{Q}_r$ = the proportion of affected sporadics in the secondary generation, from sibships of size r, who are married.

Let Q_r = the proportion of unaffected sporadics in the secondary generation, from sibships of size r, who are married, *or*, in the case of a recessive, the proportion of all unaffected persons in the secondary generation, from sibships of size r, who are married.

Let L = the proportion of all propositi in the secondary generation, from sibships of size two or greater, who are familials.

Let $L_{(m)}$ = the proportion of all married propositi in the secondary generation, from sibships of size two or greater, who are familials.

Let L_M = the proportion of all male propositi in the secondary generation, from sibships of size two or greater, who are familials.

Let $L_{(m)M}$ = the proportion of all married male propositi in the secondary generation, from sibships of size two or greater, who are familials.

Let ℓ = the proportion of *all* affected in the secondary generation, from sibships of size two or greater, who are familials.

$\ell_{(m)}$ and $\ell_{(m)M}$ are analogous with $L_{(m)}$ and $L_{(m)M}$

2. Remarks

(a) The definitions of familial, sporadic, primary generation, etc., are given in Section III. The conditions of sampling are given in Sections III and VII.

(b) The W_r and w_r estimates are awkward to define in words. If, in the case of a rare dominant, for example, there are $\bar{S}_r$ unaffected sporadics in the secondary generation who produce $\bar{A}_r$ children, then $W_r = \dfrac{\bar{A}_r}{\bar{S}_r}$.

(c) The subscripts (m) and M are used to denote that a particular statistic should be computed only on the basis of males or married persons, or, when they are together, only on the married males. Thus, $x_{r(m)M}$ is the proportion of married affected males (in the secondary generation) who come from sibships of size r, and w_{rM} is the average number of children per affected male in the secondary generation. Whenever there might be ambiguity, the symbols are explicitly defined under definitions.

In each case, the formula for females is precisely analogous to the one for males.

(d) All the statistics in the table refer only to the sibship of the propositi, and the W_r and w_r values, as well as the Q's, q's, etc., describe the history and fertility of the propositi and their sibs—*not* collaterals and *not* more distant relatives.

(e) The summations are from r = 2 to r = R, where R is the largest sibship size.

B. Variances

The sampling variances of the estimates are given in Table 2. The following is intended as a guide to Table 2.

1. Definitions of symbols

We shall confine ourselves to symbols not already given in Table 1.

Let N = the total number of known affected sibs in secondary generation sibships containing a propositus.

Let n = the total number of secondary generation sibships (i.e., sibships containing a propositus) in the sample.

Let Z_r = the sampling variance of the mean fertility of unaffected sporadics in the secondary generation from sibships of size r, *or*, in the case of a recessive, the sampling variance of the mean fertility of unaffected in sibships of size r.

Let $\hat{Z}_r$ = the sampling variance of the mean fertility of affected sporadics in the secondary generation who come from sibships of size r.

Let z_r = the sampling variance of the mean fertility of affected familials in the secondary generation who come from sibships of size r, or, in the case of a recessive, the sampling variance of the mean fertility of affected in the secondary generation who come from sibships of size r.

The Z and z values are the sampling variances of the sibship-size-specific means. They may be computed empirically from the data—that is, $\hat{Z}_r$, for example, can be computed as the sum of squares, about W_r, of the fertilities of affected sporadics in sibships of size r, divided by $m_{.r}(m_{.r} - 1)$, where $m_{.r}$ is the number of affected sporadics in sibships of size r. In symbols, if S_{ir} is the number of affected sporadics in sibships of size r who produce i children then,

$$\hat{Z}_r = \left[\sum_i S_{ir}\left(i - \sum_i \frac{S_{ir}}{S_{.r}}\right)^2\right][S_{.r}(S_{.r} - 1)]^{-1}$$

where $S_{.r} = \sum_i S_{ir}$; $\dfrac{\sum iS_{ir}}{S_{.r}} = \hat{W}_r$ of course.

Let $P_{(m)}$ = the proportion of all affected who are married.

Let $P_{(m)M}$ = the proportion of all affected males who are married.

Let $p_{(m)}$ = the proportion of all propositi who are married.

Let $p_{(m)M}$ = the proportion of all male propositi who are married.

Let $\hat{v}_r$ = the sampling variance of $\hat{Q}_r$.

Let v_r = the sampling variance of q_r.

Let $\bar{v}_r$ = the sampling variance of Q_r.

[The Q's and q's are binomial proportions. Thus, if there are S_r affected sporadics in the secondary generation from sibships of size r,

$$\hat{v}_r = \frac{\hat{Q}_r(1 - \hat{Q}_r)}{S_r}.$$

Note that $\hat{v}_{rM}$ is, of course, the sampling variance of $\hat{Q}_{rM}$. If pS_r of the S_r affected sporadics are males,

TABLE 2′—VARIANCES

Single Ascertainment

A. Rare dominant

1. Total fitness

$\text{var } w' = (1 - L)^2 f[B_r, \hat{Z}_r, \hat{W}_r, \hat{W}, (1 - L), n] + L^2 f[b_r, z_r, \hat{w}_r, \hat{w}, L, n] + g[\hat{W}, \hat{w}, L, n]$

$\text{var } W' = f[B_r, Z_r, W_r, W, (1 - L), n]$

a. Fitness of males

$\text{var } w' = (1 - L_M)^2 f[B_r, \hat{Z}_{rM}, \hat{W}_{rM}, \hat{W}_M, (1 - L), n] + L_M^2 f[b_r, z_{rM}, \hat{w}_{rM}, \hat{w}_M, L, n] + g[\hat{W}_M, \hat{w}_M, L_M, nP_M]$

$\text{var } W' = f[B_r, Z_{rM}, W_{rM}, W_{rM}, (1 - L), n]$

2. Fitness of married persons

$\text{var } w' = (1 - L_{(m)})^2 F[B_r, \hat{Z}_{r(m)}, \hat{W}_{r(m)}, \hat{W}_{(m)}, (1 - L), n, \hat{Q}_r, \hat{v}_r, \hat{D}_r, \hat{V}_r] + L_{(m)}^2 F[b_r, z_{r(m)}, \hat{w}_{r(m)}, \hat{w}_{(m)}, L, n, q_r, v_r, d_r, V_r] + G[\hat{w}_{(m)}, \hat{W}_{(m)}, L_{(m)}, np_{(m)}]$

$\text{var } W' = F[B_r, Z_{r(m)}, W_{r(m)}, W_{(m)}, (1 - L), n, Q_r, \bar{v}_r, D_r, V_r]$

a. Fitness of married males

$\text{var } w' = (1 - L_{(m)M})^2 F[B_r, \hat{Z}_{r(m)M}, \hat{W}_{r(m)M}, \hat{W}_{(m)M}, (1 - L), n, \hat{Q}_{rM}, \hat{v}_{rM}, \hat{D}_{rM}, \hat{V}_r] + L_{(m)M}^2 F[b_r, z_{r(m)M}, \hat{w}_{r(m)M}, \hat{w}_{(m)M}, L, n, q_{rM}, v_{rM}, d_{rM}, V_r] + G[\hat{w}_{(m)M}, W_{(m)M}, L_{(m)M}, np_{(m)M}]$

$\text{var } W' = F[B_r, Z_{r(m)M}, W_{r(m)M}, W_{(m)M}, (1 - L), n, Q_{rM}, \bar{v}_{rM}, D_{rM}, V_r]$

B. Rare recessive

1. Total fitness

$\text{var } w' = f[b_r, z_r, \hat{w}_r, \hat{w}, 1, n]$

$\text{var } W' = f[b_r, Z_r, W_r, W, 1, n]$

a. Fitness of males

$\text{var } w' = f[b_r, z_{rM}, \hat{w}_{rM}, \hat{w}_M, 1, n]$

$\text{var } W' = f[b_r, Z_{rM}, W_{rM}, W_M, 1, n]$

2. Fitness of married persons

$\text{var } w' = F[b_r, z_{r(m)}, \hat{w}_{r(m)}, \hat{w}_{(m)}, 1, n, q_r, v_r, d_r, V_r]$

$\text{var } W' = F[b_r, Z_{r(m)}, W_{r(m)}, W_{(m)}, 1, n, Q_r, \bar{v}_r, D_r, V_r]$

a. Fitness of married males

$\text{var } w' = F[b_r, z_{r(m)M}, \hat{w}_{r(m)M}, \hat{w}_{(m)M}, 1, n, q_{rM}, v_{rM}, d_{rM}, V_r]$

$\text{var } W' = F[b_r, Z_{r(m)M}, W_{r(m)M}, W_{(m)M}, 1, n, Q_{rM}, \bar{v}_{rM}, D_{rM}, V_r]$

Exhaustive Ascertainment

A. Rare dominant

1. Total fitness

$\text{var } w' = (1 - \ell)^2 f[X_r, \hat{Z}_r, \hat{W}_r, \hat{W}, (1 - \ell), N] + I^2 f[x_r, z_r, \hat{w}_r, \hat{w}, \ell, N] + g[\hat{W}, \hat{w}, \ell, N]$

$\text{var } W' = f[X_r, Z_r, W_r, W, (1 - \ell), N]$

a. Fitness of males

$\text{var } w' = (1 - \ell_M)^2 f[X_r, \hat{Z}_{rM}, \hat{W}_{rM}, \hat{W}_M, (1 - \ell), N] + \ell_M^2 f[x_r, z_{rM}, \hat{w}_{rM}, \hat{w}_M, \ell, N] + g[\hat{W}_M, \hat{w}_M, \ell_M, N]$

$\text{var } W' = f[X_r, Z_{rM}, W_{rM}, W_M, (1 - \ell), N]$

2. Fitness of married persons

$\text{var } w' = (1 - \ell_{(m)})^2 f[X_{r(m)}, \hat{Z}_{r(m)}, \hat{W}_{r(m)}, \hat{W}_{(m)}, (1 - \ell_{(m)}), NP_{(m)}] + \ell_{(m)}^2 f[x_{r(m)}, z_{r(m)}, \hat{w}_{r(m)}, \hat{w}_{(m)}, \ell_{(m)}, NP_{(m)}] + G[\hat{W}_{(m)}, \hat{w}_{(m)}, \ell_{(m)}, NP_{(m)}]$

$\text{var } W' = f[X_{r(m)}, Z_{r(m)}, W_{r(m)}, W_{(m)}, (1 - \ell_{(m)}), NP_{(m)}]$

a. Fitness of married males

$\text{var } w' = (1 - \ell_{(m)M})^2 f[X_{r(m)}, \hat{Z}_{r(m)M}, \hat{W}_{r(m)M}, \hat{W}_{(m)M}, (1 - \ell_{(m)}), NP_{(m)}] + \ell_{(m)M}^2 f[x_{r(m)}, z_{r(m)M}, \hat{w}_{r(m)M}, \hat{w}_{(m)M}, \ell_{(m)}, NP_{(m)}] + G[\hat{W}_{(m)M}, \hat{w}_{(m)M}, \ell_{(m)M}, NP_{(m)M}]$

$\text{var } W' = f[X_{r(m)}, Z_{r(m)M}, W_{r(m)M}, W_{(m)M}, (1 - \ell_{(m)}), NP_{(m)}]$

TABLE 2—*Continued*

Exhaustive Ascertainment—*continued*

B. Rare recessive

1. Total fitness
   var $w' = f[x_r, z_r, w_r, \hat{w}, 1, N]$
   var $W' = f[x_r, Z_r, W_r, W, 1, N]$
   a. Fitness of males
      var $w' = f[x_r, z_{rM}, \hat{w}_{rM}, \hat{w}_M, 1, N]$
      var $W' = f[x_r, Z_{rM}, W_{rM}, W_M, 1, N]$
2. Fitness of married persons
   var $w' = f[x_{r(m)}, z_{r(m)}, \hat{w}_{r(m)}, \hat{w}_{(m)}, 1, NP_{(m)}]$
   var $W' = f[x_{r(m)}, Z_{r(m)}, W_{r(m)}, W_{(m)}, 1, NP_{(m)}]$
   a. Fitness of married males
      var $w' = f[x_{r(m)}, z_{r(m)M}, \hat{w}_{r(m)M}, \hat{w}_{(m)M}, 1, NP_{(m)}]$
      var $W' = f[X_{r(m)}, Z_{r(m)M}, W_{r(m)M}, W_{(m)M}, 1, NP_{(m)}]$

$$\hat{v}_{rM} = \frac{\hat{Q}_{rM}(1 - \hat{Q}_{rM})}{pS_r},$$

so also for v_{rM} and $\bar{v}_{rM}$.]

Let $Q = \sum B_r Q_r$, $\hat{Q} = \sum B_r \hat{Q}_r$, and $q = \sum b_r q_r$ for a dominant.
Let $Q = \sum b_r Q_r$ and $q = \sum b_r q_r$, for a recessive.

Let $V_r = \frac{b_r(1 - b_r)}{nL}$ and $\hat{V}_r = \frac{B_r(1 - B_r)}{(1 - L)n}$, for a dominant.

Let $V_r = \frac{b_r(1 - b_r)}{n}$ for a recessive.

Let $D_r = W_r Q_r$, and let $D = \sum B_r D_r$ in the case of a dominant, while $D = \sum b_r D_r$ in the case of a recessive.
Let $\hat{D}_r = \hat{W}_r \hat{Q}_r$ and let $\hat{D} = \sum B_r \hat{D}_r$.
Let $d_r = \hat{w}_r q_r$ and let $d = \sum b_r d_r$.
[Note that $D_{rM} = W_{rM} Q_{rM}$ and $D_M = \sum D_{rM} B_r$, and so also for $\hat{D}_r$ and $\hat{d}_r$.]

Let $f[B_r, \hat{Z}_r, \hat{W}_r, \hat{W}, (1 - L), n]$

$$= \sum B_r^2 \hat{Z}_r + \frac{\sum B_r(\hat{W}_r - \hat{W})^2 + B_r(\hat{Z}_r - B_r \hat{Z}_r)}{(1 - L)n}.$$

Let $g[\hat{W}, \hat{w}, L, n] = \frac{L(1 - L)(\hat{w} - \hat{W})^2}{n}$, and we shall also use the slightly redundant notation,

$$G[w_{(m)}, W_{(m)}, L_{(m)}, nP_{(m)}] = \frac{L_{(m)}(1 - L_{(m)})(\hat{w}_{(m)} - \hat{W}_{(m)})^2}{nP_{(m)}}.$$

Let $F[B_r, \hat{Z}_{r(m)}, \hat{W}_{r(m)}, \hat{W}_{(m)}, (1 - L), n, \hat{Q}_r, \hat{v}_r, \hat{D}_r, \hat{V}_r] = E_1 - 2\hat{W}_{(m)}E_{12} + \hat{W}^2_{(m)}E_2$, where

$$E_1 = \left[\sum (\hat{Z}_{r(m)}\hat{Q}_r^2 + \hat{W}^2_{r(m)}\hat{v}_r)(B_r^2 + \hat{V}_r) + \sum \hat{Z}_{r(m)}B_r^2\hat{v}_r + \sum \frac{B_r(\hat{D}_r - \hat{D})^2}{(1 - L)n}\right](\sum \hat{Q}_r B_r)^{-2},$$

where

$$E_{12} = \left[\sum \hat{W}_{r(m)}\hat{v}_r(B_r^2 + \hat{V}_r) + \sum Q_r B_r \frac{(\hat{D}_r - \hat{D})^2}{(1 - L)n}\right](\sum \hat{Q}_r B_r)^{-2},$$

and where

$$E_2 = \left[\sum \hat{v}_r(B_r^2 + \hat{V}_r) + \sum B_r \frac{(\hat{Q}_r - \hat{Q})^2}{(1 - L)n}\right](\sum \hat{Q}_r B_r)^{-2}.$$

The functional notation is used to save space. It will be understood in Table 2 that when we substitute, say, q_r for $\bar{Q}_r$ in the function, we are also substituting q for $\bar{Q}$—and similarly for the D's.

2. Remarks

The conventions regarding subscripts, summation, etc. are the same as those given for the table of estimators (Table 1).

C. Covariances and biases

Expressions for the covariances and biases are set out in Table 3.

1. Definition of symbols

a. General

Let

$$h[B_r, W_{r(m)}, W_{(m)}, \hat{W}_{r(m)}, \hat{W}_{(m)}, Q_r, \hat{Q}_r, (1 - L), n, D_r, \hat{D}_r] = W_{(m)}\hat{W}_{(m)}c_2 - \hat{W}_{(m)}c_{12} - W_{(m)}c_{21} + c_1,$$

where

$$c_2 = [(\sum Q_r B_r \sum \hat{Q}_r B_r)(1 - L)n]^{-1} \sum Q_r B_r(\hat{Q}_r - \hat{Q}),$$

where

$$c_{12} = [(\sum Q_r B_r \sum \hat{Q}_r B_r)(1 - L)n]^{-1} \sum W_{r(m)} Q_r B_r(\hat{Q}_r - \hat{Q}),$$

where

$$c_{21} = [(\sum Q_r B_r \sum \hat{Q}_r B_r)(1 - L)n]^{-1} \sum \hat{W}_{r(m)} \hat{Q}_r B_r(Q_r - Q),$$

TABLE 3.—BIASES AND COVARIANCES

Single ascertainment

A. Rare dominant

1. Total fitness

$w'(\text{bias}) = 0$

$W'(\text{bias}) = 0$

$\text{cov } w', W' = \Sigma \hat{W}_r B_r (W_r - W) n^{-1}$

a. Fitness of males

$w'(\text{bias}) = 0$

$W'(\text{bias}) = 0$

$\text{cov } w', W' = (1 - L_M)\Sigma W_{rM}, B_r(W_{rM} - W_M)[(1 - L)n]^{-1}$

2. Fitness of married persons

$w'(\text{bias}) = L_{(m)}(\hat{w}_{(m)}E_2 - E_{12}) + (1 - L_{(m)})(\hat{W}_{(m)}E_2 - E_{12})$

$W'(\text{bias}) = W_{(m)}E_2 - E_{12}$

$\text{cov } w', W' = (1 - L_{(m)})h[B_r, W_{r(m)}, W_{(m)}, \hat{W}_{r(m)}, \hat{W}_{(m)}, Q_r, \hat{Q}_r, (1 - L), n, D_r, \hat{D}_r]$

a. Fitness of married males

$w'(\text{bias}) = L_{(m)M}(\hat{w}_{(m)M}, E_2 - E_{12}) + (1 - L_{(m)M})(\hat{W}_{(m)M}E_2 - E_{12})$

$W'(\text{bias}) = W_{(m)M}E_2 - E_{12}$

$\text{cov } w', W' = (1 - L_{(m)M})h[B_r, W_{r(m)M}, W_{(m)M}, \hat{W}_{r(m)M}, \hat{W}_{(m)M}, Q_{rM}, \hat{Q}_{rM}, (1 - L), n, D_{rM}, \hat{D}_{rM}]$

B. Rare recessive

1. Total fitness

$w'(\text{bias}) = 0$

$W'(\text{bias}) = 0$

$\text{cov } w', W' = \Sigma \hat{w}_r b_r (W_r - W) n^{-1}$

a. Fitness of males

$w'(\text{bias}) = 0$

$W'(\text{bias}) = 0$

$\text{cov } w', W' = \Sigma \hat{w}_{rM} b_r (W_{rM} - W_M) n^{-1}$

2. Fitness of married persons

$w'(\text{bias}) = \hat{w}_{(m)}E_2 - E_{12}$

$W'(\text{bias}) = W_{(m)}E_2 - E_{12}$

$\text{cov } w', W' = h[b_r, W_{r(m)}, W_{(m)}, w_{r(m)}, w_{(m)}, Q_r, q_r, 1, n, D_r, d_r]$

a. Fitness of married males

$w'(\text{bias}) = w_{(m)M}E_2 - E_{12}$

$W'(\text{bias}) = W_{(m)}E_2 - E_{12}$

$\text{cov } w', W' = h[b_r, W_{r(m)M}, W_{(m)M}, w_{r(m)M}, w_{(m)M}, Q_{rM}, q_{rM}, 1, n, D_{rM}, d_{rM}]$

Exhaustive ascertainment

A. Rare dominant

1. Total fitness

$w'(\text{bias}) = 0$

$W'(\text{bias}) = 0$

$\text{cov } w', W' = \Sigma \hat{W}_r X_r (W_r - W) N^{-1}$

a. Fitness of males

$w'(\text{bias}) = 0$

$W'(\text{bias}) = 0$

$\text{cov } w', W' = (1 - \ell_M)\Sigma \hat{W}_{rM} X_r (W_{rM} - W_M)[(1 - \ell)N]^{-1}$

2. Fitness of married persons

$w'(\text{bias}) = 0$

$W'(\text{bias}) = 0$

$\text{cov } w', W' = \Sigma \hat{W}_{r(m)} X_{r(m)} (W_{r(m)} - W_{(m)})(NP_{(m)})^{-1}$

TABLE 3—*Continued*

Exhaustive Ascertainment—*Continued*

a. Fitness of married males
$w'(\text{bias}) = 0$
$W'(\text{bias}) = 0$
$\text{cov } w', W' = (1 - \ell_{(m)M})\Sigma\hat{W}_{r(m)M}X_{r(m)}(W_{r(m)M} - W_{(m)M})[(1 - \ell_{(m)})NP_{(m)}]^{-1}$

B. Rare recessive
1. Total fitness
$w'(\text{bias}) = 0$
$W'(\text{bias}) = 0$
$\text{cov } w', W' = \Sigma\hat{W}_r x_r(W_r - W)N^{-1}$
a. Fitness of males
$w'(\text{bias}) = 0$
$W'(\text{bias}) = 0$
$\text{cov } w', W' = \Sigma\hat{W}_{rM}x_r(W_{rM} - W_M)N^{-1}$
2. Fitness of married persons
$w'(\text{bias}) = 0$
$W'(\text{bias}) = 0$
$\text{cov } w', W' = \Sigma\hat{W}_{r(m)}x_{r(m)}(W_{r(m)} - W_{(m)})(NP_{(m)})^{-1}$
a. Fitness of married males
$w'(\text{bias}) = 0$
$W'(\text{bias}) = 0$
$\text{cov } w', W' = \Sigma\hat{W}_{r(m)M}x_{r(m)}(W_{r(m)M} - W_{(m)M})(NP_{(m)})^{-1}$

and where

$$c_1 = [(\sum Q_r B_r \sum \hat{Q}_r B_r)(1 - L)n]^{-1} \sum B_r \hat{D}_r(D_r - D).$$

It will again be understood that when we substitute, say, q_r for $\hat{Q}_r$ in the function, we are also substituting q for $\bar{Q}$—and, again, similarly for the D's.

b. E-values

The other symbols in Table 3 have all been defined in connection with Tables 1 and 2. The E's occurring in the bias expression have no general definition, but are obtained from the particular functions occurring in Table 2. To obtain the appropriate definition of E_{12} and E_2, follow these rules:

(1) Locate the variance function under the headings in Table 2 which correspond to the headings of the E-values in Table 3. If only one variance function is given, then the E-values are obtained from that function.

(2) If two or more functions are given in Table 2, then the function in Table 2 which has the coefficient $(1 - L_{(m)})^2$ is appropriate for the E-values in Table 3 which have the coefficient $(1 - L_{(m)})$, and, similarly, the function in Table 2 which has the coefficient $L_{(m)}^2$ is appropriate for the E-values with coefficient $L_{(m)}$. The same rule holds for $L_{(m)M}$.

Example: In Table 3, under the headings, single ascertainment, and fitness of married males, we find, under w′ (bias),

$$L_{(m)M}(\hat{W}_{(m)M}E_2 + E_{12}) + (1 - L_{(m)M})(\hat{W}_{(m)M}E_2 + E_{12}).$$

TABLE 4.—GENERAL FORMULAE

1) Estimate of Partial Mean Fitness of Affected $= \dfrac{w'}{W'}$

2) Bias in $\dfrac{w'}{W'} = \dfrac{w'}{W'^2}\ \text{var}\ W - \dfrac{\text{cov}\ w', W'}{W'^2}$

3) $\text{var}\left(\dfrac{w'}{W'}\right) = W'^{-2}\left[\dfrac{w'^2}{W'^2}\ \text{var}\ W' - 2\,\dfrac{w'}{W'}\ \text{cov}\ (w', W') + \text{var}\ w'\right]$

4) If T′ is a biased estimate, and T is an unbiased estimate, then the bias, β, is defined

$$\beta = T' - T, \text{ so that } T = T' - \beta.$$

In Table 2, under single ascertainment, fitness of married males, we find, under var (w′), that

$$F(B_r\ ,\ \hat{Z}_{r(m)M}\ ,\ \hat{W}_{r(m)M}\ ,\ \hat{W}_{(m)M}\ ,\ (1 - L),\ n,\ \hat{Q}_{rM}\ ,\ \hat{v}_{rM}\ ,\ D_{rM}\ ,\ \hat{V}_r)$$

is the coefficient of $(1 - L_{(m)M})^2$ so that (remembering the definitions of the E-values given in connection with Table 2) the coefficient of $\hat{W}^2_{(m)}$ in this function, is the appropriate value of E_2, and the coefficient of $2W_{(m)}$ in the function is the appropriate value of E_{12} to be substituted into the expression $(1 - L_{(m)M})(\hat{W}_{(m)M}E_2 + E_{12})$. In the same way the definitions of E_2 and E_{12} in the expression $L_{(m)M}(\hat{W}_{(m)M}E_2 + E_{12})$ can be found.

2. *Remarks*

The biases which occur in these statistics are always small compared with the sampling error. If one has already computed the appropriate E-values to obtain the variance, then the bias can be obtained almost instantly, and it is certainly worthwhile to compute it. On the other hand, it is not worthwhile to compute E-values solely for the purpose of evaluting the bias.

D. *General formulae*

Formulae appropriate in all cases considered here, for estimating fitness, its bias, and variance, are set out in Table 4. Not that the bias in the estimate of fitness will persist, even if the estimates it is computed from are unbiased statistics, that is, even if W and w are unbiased, or if the bias has been removed from them. However, the bias in w/W is small compared with the sampling error.

The definition for bias given here is the one that has been used throughout the derivations. To reduce the bias of an estimate, one *subtracts* the estimate of the bias.

E. *Additional notes*

1. *The complexity of the variances*

The variances given in Table 2 are surprisingly complicated. In view of their complexity, many workers may wish to content themselves with the estimates, and perhaps find very rough measures of the order magnitude of the variances. At the present time, it is probably not too important to be able to measure the variance of

TABLE 5.—APPROXIMATE ORDERS OF MAGNITUDE OF SEVERAL OF THE VARIANCES AND COVARIANCES

System of Ascertainment	Condition	var w′	var W′	cov w′, W′
Single ascertainment	A. Rare dominant			
	1. Total fitness	$\nabla\left(\frac{n}{1-L}, \frac{n}{L}\right)$	$[(1-L)n]^{-1}$	n^{-1}
	a. Fitness of males	$\nabla\left(\frac{(1-L)n}{(1-L_M)^2}, \frac{Ln}{L_M^2}\right)$	$[(1-L)n]^{-1}$	$[(1-L)n]^{-1}$
	B. Rare recessive			
	1. Total fitness	n^{-1}	n^{-1}	n^{-1}
	a. Fitness of males	n^{-1}	n^{-1}	n^{-1}
Exhaustive ascertainment	A. Rare dominant			
	1. Total fitness	$\nabla\left(\frac{N}{1-\ell}, \frac{N}{\ell}\right)$	$[(1-\ell)N]^{-1}$	N^{-1}
	a. Fitness of males	$\nabla\left(\frac{(1-\ell)N}{(1-\ell_M)^2}, \frac{lN}{\ell_M^2}\right)$	$[(1-\ell)N]^{-1}$	$(1-\ell_M)[(1-\ell)N]^{-1}$
	2. Fitness of married persons	$\nabla\left(\frac{NP_{(m)}}{1-\ell_{(m)}}, \frac{NP_{(m)}}{\ell_{(m)}}\right)$	$[(1-\ell_{(m)})NP_{(m)}]^{-1}$	$(NP_{(m)})^{-1}$
	a. Fitness of married males	$\nabla\left(\frac{(1-\ell_{(m)})NP_{(m)}}{(1-\ell_{(m)M})^2}, \frac{\ell_{(m)}NP_{(m)}}{\ell_{(m)M}^2}\right)$	$[(1-\ell_{(m)})NP_{(m)}]^{-1}$	$(1-\ell_{(m)M})[(1-\ell_{(m)})NP_{(m)}]^{-1}$
	B. Rare recessive			
	1. Total fitness	N^{-1}	N^{-1}	N^{-1}
	a. Fitness of males	N^{-1}	N^{-1}	N^{-1}
	2. Fitness of married persons	$(NP_{(m)})^{-1}$	$(NP_{(m)})^{-1}$	$(NP_{(m)})^{-1}$
	a. Fitness of married males	$(NP_{(m)})^{-1}$	$(NP_{(m)})^{-1}$	$(NP_{(m)})^{-1}$

Notation: $\nabla(a, b)$ is (defined as) equal to the reciprocal of the *smaller* of the two elements in the vector (a, b).

an estimated fitness with great precision, provided the fitness is quite small or quite large. If, however, the fitness is in the neighborhood of one, the variance may prove important, since qualitative statements about the expected increase or decrease of the frequency of the gene are often based upon whether the estimate exceeds or is less than one. It is clearly desirable to know, at least approximately, the significance of the departure from one.

2. Short-cuts; orders of magnitude

An effort was made in presenting the tables to employ a notation which would be consistent from entry to entry and from table to table. This has, inevitably, concealed some of the relations.

It should be noted that the over-all average fertility (without respect to sibship size) frequently occurs, in the expressions for the fertility of affected. (It *never* occurs in the expressions for the fertility of unaffected.) This should simplify the computation of the estimates. Thus, the over-all average fertility of affected sporadics is identical with $\sum \hat{W}_r B_r$, and the over-all average fertility of married affected sporadics is identical with $\frac{\sum W_r Q_r B_r}{\sum Q_r B_r}$. These over-all averages occur most frequently in the estimates of the fertility of affected under exhaustive ascertainment,* where almost all of the estimates are such averages. Unhappily this does not simplify the variances.

Orders of magnitude have not yet been worked out for all the variances in Table 2 and all the covariances in Table 3. In some cases, they have, however, and the available ones are given in Table 5. The orders are estimated on the assumption that information about the parameter is very large. The estimates are *rough*.

NUMERICAL EXAMPLES

Numerical examples of some of the formulae may be found in Crowe, Schull, and Neel (1954).

SUMMARY

Problems which arise in the estimation of fitness from affected children and their sibs are discussed. Estimators of fitness, together with their biases and variances are developed. Some more general but related problems in the estimation of fitness in man are also discussed. A computer's summary is given in Section XI.

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* The exceptions occur when a sex is separated out. If one chose to use x_{rM} and $x_{r(m)M}$ as the weighting factors, rather than x_r and $x_{r(m)}$, the estimates of the fertility of affected would here also become over-all averages.

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The Dynamics of Racial Intermixture in the American Negro—Some Anthropological Considerations

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THE RECENT DEVELOPMENT, by Drs. Bentley Glass and C. C. Li (1953), of a method making use of gene frequencies for the study of the dynamics of race mixture is a welcome contribution to the genetic aspects of anthropological research. By the application of this method, the authors estimate the average rate of gene flow into the American Negro per generation from the White population, assuming ten generations of intermixture, to be .0358; the accumulated amount of White admixture in their American Negro sample is calculated to be 30.6%. The following note endeavours to amplify their conclusions in the light of information more recently available.

The use in their communication of gene frequencies pertaining to South African Bantu, East Africans and Sudanese was satisfactory for demonstration of the statistical model; Glass and Li had of necessity to include these in their calculations on account of the paucity of data then to hand. Acceptance of the gene flow values so obtained however implies that it is immaterial whence the African parental population gene frequencies are derived. That there is a "high degree of uniformity in the distribution of the Rh and MNS groups throughout tropical Africa" does not mean that Rh chromosome frequencies are constant throughout Negro Africa, but only that the overall pattern is generally similar. Thus in every sample yet investigated from Africa south of the Sahara, chromosome cDe is the most frequent, yet its calculated frequency varies between .34 and .82; cde is the second most frequent in more than 85% of samples, yet its value varies from .13 to .28. On the other hand frequencies of the genes of the MN blood group system do tend to be less variable, and much of the variation observed from sample to sample could be explained as random effects in sampling, though there is a slight tendency for the M frequency to increase from west to east. Statistically significant differences occur in the ABO frequencies, which in East Africa for example serve to distinguish the major ethnic subdivisions of the peoples. By reason of these variations, for computations involving actual blood group frequencies, such as are required by Glass and Li's method, it is obvious that in addition to the question of choice of characters to discriminate most clearly between the parental populations, attention has to be given to the choice of population whose gene frequencies are to represent the African parental contribution.

The extensive researches of Herskowits (1928, 1933, 1942) showed that the provenance of the Negro slaves in the U.S.A. was of more limited area than had been earlier thought. A few were derived from Madagascar and east coast localities, but the large majority originated from the western regions of Africa. The coastlands and a broad belt of territory behind them, in places several hundred miles in depth, ex-

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tending from Gambia in the north to Angola in the south, provided the bulk of the American slaves. There was a shift in supply from area to area throughout the slaving period, and it is impossible to estimate the proportions of the different African peoples who contributed to the American Negro genetic constitution. Nevertheless the problem relates to an essentially western African population. It is from peoples occupying this zone that the gene frequencies should be drawn for the African parental population in the study of American Negro hybridization.

Relevant to the problem are comprehensive Rh data for four samples from different parts of Nigeria (Chalmers Ikin & Mourant, 1953) and two from the Gold Coast, for Ashanti and Ewe (Armattoe Ikin & Mourant, 1953), examined at the Blood Group Reference Laboratory, London, together with a second for the Ewe (Armattoe, 1951) referred to by Glass & Li; two samples from the lower Congo (Lambotte-Legrand, 1950) give simple Rh positive and negative data. Information on the MN blood group system is given for all except the two Congo samples, the Ss subdivisions being included among the Nigerian data. Data for the ABO system are to hand for more than than a dozen relevant samples, while several studies have been made, mainly on composite samples from West Africa, of the less widely investigated blood groups. Altogether there are now available frequencies of some twenty genes or gene combinations which allow comparisons of western Africans, American Negroes and American Whites.

From these data the gene flow rate into the American Negro has been recalculated, assuming ten generations of intermixture. In the Rh calculations allowance was made where possible for the fact that where no D^u tests are done possessors of the D^u gene may be classified as d (Mourant, 1954).

Table 1 shows the estimates of average gene flow rate obtained from the five genes or chromosomes that give the clearest discrimination between the parental populations—discrimination being assessed in terms of the minimum interval between the frequencies obtained in samples of the parental groups. The five characters are arranged in descending order of their discriminatory value. It is interesting that the trend of these estimates is considerably below those found by Glass & Li, the modal value of gene flow rate now occurring between .02 and .025. Plotting of 200 positive estimates obtained from seventeen genes or chromosomes, of which more than half are of little discriminatory value, gives a similar mode, though the range is considerably greater. The amount of White admixture (table 2) is likewise lower than previous estimates, the modal value, for the five characters given in table 1, lying between 18 and 22%. The estimate derived from the phenylthiocarbamide taste gene (T) probably may not be as reliable as its position in the table seems to suggest since the West African sample on which it is based, that of Barnicot (1950), comprised only 57 individuals. The gene frequencies used in the computations and the size of sample from which they were derived are given in table 3.

These figures for gene flow rate and intermixture must again be regarded as provisional. In addition to the difficulties noted by Glass & Li, there is no possibility of weighting the African frequencies to compensate for the different proportions of these peoples who were transported to the U.S.A. The estimates obtained for the gene flow rate from data relating to small local samples of American Negroes should

TABLE 1.—AVERAGE RATES OF GENE FLOW PER GENERATION, ASSUMING TEN GENERATIONS OF INTERMIXTURE, FROM THE AMERICAN WHITE INTO THE AMERICAN NEGRO POPULATION AS REPRESENTED BY SIX SAMPLES

African sample used	American Negro Sample								
	Baltimore[6]		Washington[7]		Ohio[8] and Southern	New York[9]		New York[10]	Michigan(?)[11]
	Estimate 1[12]	Estimate 2[13]	Estimate 1[12]	Estimate 2[13]		Estimate 1[14]	Estimate 2[15]		
R^o (Rh blood group system)									
Ewe[1]	.0214	.0215	.0208	.0209					
Ewe[2]	.0078	.0078	.0072	.0072					
Ashanti[2]	.0235	.0236	.0228	.0229					
S.W. Nigeria[3]	.0312	.0314	.0306	.0307					
S.E. Nigeria[3]	.0244	.0245	.0237	.0239					
Jos plateau[3]	.0253	.0254	.0246	.0248					
N. Nigeria[3]	.0199	.0200	.0191	.0194					
T (PTC taste)									
W. Africa[4]					.0384				
R^1 (Rh blood group system)									
Ewe[1]	.0219	.0210	.0208	.0198					
Ewe[2]	.0192	.0184	.0183	.0174					
Ashanti[2]	.0087	.0083	.0076	.0073					
S.W. Nigeria[3]	.0271	.0260	.0262	.0250					
S.E. Nigeria[3]	.0303	.0288	.0293	.0280					
Jos plateau[3]	.0398	.0383	.0388	.0373					
N. Nigeria[3]	.0154	.0147	.0143	.0137					
Jk^b (Kidd blood group system)									
W. Africa[5]						.0221	.0215		
S (MNS blood group system)									
S.W. Nigeria[3]								.0183	.0246
S.E. Nigeria[3]								.0237	.0300
Jos plateau[3]								—	.0041
N. Nigeria[3]								.0112	.0175

[1] Armattoe 1951 (gene frequencies calculated by Glass and Li 1953, Table 3).
[2] Armattoe, Ikin, and Mourant 1953.
[3] Chalmers, Ikin, and Mourant 1953.
[4] Included in results of Barnicot 1950.
[5] Ikin and Mourant 1952.
[6] Glass and Li 1953.
[7] Moore 1955.
[8] Lee 1934, using American White gene frequency of Snyder 1932.
[9] Rosenfield, Vogel, Gibbel, Ohno, and Haber 1953.
[10] Miller, Rosenfield, and Vogel 1951.
[11] Neel and Hanig 1951, using American White gene frequencies of Wiener, Di Diego, and Sokol 1953.
[12] Using American White gene frequencies of Unger, Weinberg, and Lefkon 1946.
[13] Using American White gene frequencies of Wiener 1945.
[14] Using American White gene frequencies of Allen, Diamond, and Niedziela 1951.
[15] Using American White gene frequencies of Rosenfield, Vogel, Gibbel, Ohno, and Haber 1953.

TABLE 2.—PERCENTAGE OF WHITE ADMIXTURE IN THE AMERICAN NEGRO SAMPLES OF TABLE 1

African sample used	American Negro Sample								
	Baltimore		Washington		Ohio and Southern	New York		New York	Michigan (?)
	Estimate 1	Estimate 2	Estimate 1	Estimate 2		Estimate 1	Estimate 2		
R^o									
Ewe	19.46	19.58	18.88	18.99					
Ewe	7.53	7.57	6.86	6.90					
Ashanti	21.14	21.26	20.57	20.68					
S.W. Nigeria	27.17	27.32	26.66	26.80					
S.E. Nigeria	21.88	22.00	21.31	21.43					
Jos plateau	22.59	22.71	22.04	22.16					
N. Nigeria	18.19	18.30	17.61	17.72					
T									
W. Africa					32.41				
R^1									
Ewe	19.83	19.05	18.95	18.21					
Ewe	17.67	16.95	16.77	16.09					
Ashanti	8.34	7.96	7.33	7.01					
S.W. Nigeria	24.03	23.14	23.20	22.34					
S.E. Nigeria	26.47	25.51	25.67	24.74					
Jos plateau	33.41	32.31	32.69	31.62					
N. Nigeria	14.33	13.72	13.40	12.84					
Jk^b									
W. Africa						20.00	19.56		
S									
S.W. Nigeria								16.90	22.07
S.E. Nigeria								21.34	26.23
Jos plateau								—	4.04
N. Nigeria								10.61	16.17

not be taken as representative of the whole American Negro population. It appears doubtful to assume that there has been no change in the gene frequencies of the populations concerned. Glass & Li have noted the possibility of different selective forces under African and American conditions. Historical facts have also to be taken into account. For example, concerning the White population, the pattern of immigration into the U.S.A. within the last century shows how the proportions of immigrants contributed by different regions of Europe has varied, with consequent fluctuation in gene frequencies of the White parental population. There should also be considered the tendency for particular European groups to settle in particular regions of the U.S.A., especially in the earlier days, with consequent restriction of potential hybridization to only part of the White population. Such effects however on the genes listed in the table may well have been slight.

Finally the assumption is made that the American Negro is the product of hybridization between two, and only two, parental populations, an assumption noted with reference to the American Indian by Stern (1953). In Meier's (1949) sample, 69% of his Mississippi born Negroes were recorded as having some American Indian

TABLE 3.—GENE FREQUENCIES FROM WHICH THE ESTIMATES IN TABLES 1 AND 2 WERE CALCULATED

African			American Negro			American White		
Sample	Sample size	Gene frequency	Sample	Sample size	Gene frequency	Sample	Sample size	Gene frequency
				R^o				
Ewe[1]	853	.547	Baltimore[6]	907	.446	New York[12]	7317	.028
Ewe[2]	161	.480	Washington[7]	937	.449	New York[13]	1000	.031
Ashanti[3]	113	.558						
S.W. Nigeria[3]	145	.602						
S.E. Nigeria[3]	106	.563						
Jos plateau[3]	124	.568						
N. Nigeria[3]	165	.539						
				T				
W. Africa[4]	57	.813	Ohio and Southern[8]	3156	.697	Ohio[14]	3643	.455
				R^1				
Ewe[1]	853	.077	Baltimore[6]	907	.145	New York[12]	7317	.420
Ewe[2]	161	.086	Washington[7]	937	.142	New York[13]	1000	.434
Ashanti[3]	113	.120						
S.W. Nigeria[3]	145	.058						
S.E. Nigeria[3]	106	.046						
Jos plateau[3]	124	.007						
N. Nigeria[3]	165	.099						
				Jk^b				
W. Africa[5]	85	.217	New York[9]	305	.269	Boston[15]	189	.477
						New York[16]	726	.483
				S				
S.W. Nigeria[3]	112	.124	New York[10]	580	.160	New York[17]	394	.337
S.E. Nigeria[3]	57	.112	Michigan[11]	96	.171			
Jos plateau[3]	123	.164						
N. Nigeria[3]	159	.139						

[1] Armattoe 1951 (gene frequencies calculated by Glass and Li 1953, Table 3)
[2] Armattoe, Ikin, and Mourant 1953.
[3] Chalmers, Ikin, and Mourant 1953.
[4] Included in results of Barnicot 1950.
[5] Ikin and Mourant 1952.
[6] Glass and Li 1953.
[7] Moore 1955.
[8] Lee 1934.
[9] Rosenfield, Vogel, Gibbel, Ohno, and Haber 1953.
[10] Miller, Rosenfield, and Vogel 1951.
[11] Neel and Hanig 1951.
[12] Unger, Weinberg, and Lefkon 1946.
[13] Wiener 1945.
[14] Snyder 1932.
[15] Allen, Diamond, and Niedziela 1951.
[16] Rosenfield, Vogel, Gibbel, Ohno, and Haber, 1953.
[17] Wiener, Di Diego, and Sokol 1953.

ancestry, while in Herskowits' (1930) sample, mainly from the mid Atlantic and southeastern states, 27% were so recorded. None of the few American Indian tribes whose serology has as yet been investigated in detail is likely to have made an important contribution to the American Negro hybrid, and known regional differences in blood group frequency among Indian tribes preclude accurate estimates of the gene frequencies which Indians of the South and East must have contributed. However the general pattern of gene frequency, as regards the characters listed in the table, may perhaps be inferred from what is known for Indians of the Plains and the South West. Only for gene T does the frequency found in the American Indian resemble that of the African—and it has been pointed out above that the estimate of intermixture here derived from this character may not be very reliable. Otherwise, as regards frequencies of R^o, R', Jk^b, and S, the American Indian tends to be much more similar to the European than to the African; in each does the hybrid frequency fall intermediately between the African figure on the one hand and those of the European and American Indian on the other. That is to say that for these characters the shift in gene frequency of the American Negro away from that of the African is due to the combined effect of European and Indian admixture, each reinforcing not counteracting the other. It therefore appears that the above estimates of the European contribution to the American Negro gene-pool may be too high, by a greater or lesser degree proportional to the magnitude of the Indian contribution.

SUMMARY

The average gene flow rate per generation from the American White population into the American Negro population has been recalculated using data from western Africa, the region whence the majority of the Negro slaves were derived, to represent the African parental population. The modal value for gene flow rate assuming ten generations of intermixture falls between .02 and .025, while the amount of accumulated White admixture is estimated as about 20%. That these estimates are provisional has been stressed.

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On the Unlikelihood of Significant Admixture of Genes from the North American Indians in the Present Composition of the Negroes of the United States

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GLASS AND LI (1953), in their first effort to examine the dynamics of racial intermixture, deliberately oversimplified the interplay of factors responsible for the present status of the North American Negro, in order to construct a model that in principle would exemplify the effects of gene flow between populations. Two aspects of their simplified model have received a certain amount of criticism. In the first place, although they implicitly recognized that the great majority of the slaves brought to North America were derived from West Africa, yet, in the absence of data on the frequencies of certain blood groups among West African natives, they utilized frequencies from Bantu (MN; Rh), from East African tribes (Rh; PTC taste capacity), and from the Sudan (PTC taste capacity). This was done in the hope that PTC taste capacity, like the Rh and MNS blood groups, would, in Mourant's words, prove to reveal a "high degree of uniformity in the distribution . . . throughout tropical Africa" (pers. commun.). Now that Chalmers, Ikin, and Mourant (1953) have published data on four geographical groups of Nigerians, and Armattoe, Ikin, and Mourant (1953) have supplied further data on the Ewe and Ashanti of the Gold Coast, it seems desirable to recheck the original calculations in order to see whether the estimates of the amount of White admixture in the North American Negro and the gene flow per generation were seriously in error.

In the second place, Stern (1953) and others (Sturtevant, pers. commun.) have remarked on the failure in our original treatment to take into account the considerable amount of genetic admixture between the American Indians and the North American Negro populations. Herskovits (1930) and Meier (1949) have been cited to indicate the very high proportion of Negro college students who claim some American Indian ancestry. Stern has justly criticized the generality and validity of these data. They may possibly apply better to the Mississippi Valley region than to the Eastern United States. More important is the fact that a very few American Indian ancestors seven to ten generations back might have numerous descendants in the North American Negro population of the present day. Clearly, the number of persons who claim to have at least one American Indian ancestor yields no clue whatsoever to the amount of gene flow from the Indian into the Negro population, particularly during the more recent generations.

The recent publication of the blood group frequencies of the Chippewa Indians of Northern Minnesota, by Matson, Koch, and Levine (1954), supplies somewhat

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better data for estimating the American Indian contribution to the North American Negro gene pool than previously existed, although obviously if we had data on the blood group frequencies of the Cherokees or the Iroquois, these would be even better. The Chippewas themselves almost certainly never intermingled with the North American Negroes to any great extent, if at all; and the allele frequencies among the Chippewas can only be taken as substitutes for those of the more eastern and southern tribes. These are in most cases now so broken up and so intermixed with White genetic elements that it may never be possible to find a reliable sample of the original Indian tribes. The Chippewas at least indicate the chief features of the Eastern and Southern tribes better than the Southwestern tribes (Navaho, Apache, Pueblo Indians) would be likely to do; and the classification of the Chippewas into "pure," "$>3/4$" "$<3/4$" enables one, as with no other set of data, to use in the calculations values approximating those of the aboriginal American Indians.

The central, crucial estimate in these calculations is that of the frequency of the R^o (*cDe*) allele, because of the tremendous difference between its frequencies in the West African and the White populations. It is also of special importance that the R^o frequencies in the Whites (0.028) and Amerindians (0.000) scarcely differ at all. The R^o frequencies can therefore be utilized to calculate the total genetic change between the West African and the North American Negroes, *irrespective of the relative magnitudes of the contributions to the hybrid population made by Whites and Amerindians*. Hence it is possible to test the problematical contribution of the Amerindians by first calculating expectancies for each gene on the basis of the hypothesis that all the shift in the R^o frequency from the West African value to the North American Negro value has been produced by admixture with the White population, and then checking these expectancies against the actual frequencies observed in the North American Negro population. Several situations arise: (a) when W. African and White frequencies are the same and the Amerindian frequency is different; (b) when the White and Amerindian frequencies deviate from the W. African frequencies in the same direction but to a different degree; and (c) when the White and Amerindian frequencies deviate from the W. African frequency in opposed directions.

A REESTIMATION OF THE GENE FLOW BETWEEN N. AMERICAN WHITE AND NEGRO POPULATIONS

The former estimate of the frequency of the R^o allele among African Negroes was 0.630 (Glass and Li, 1953), derived from the value for the East Africans given by Donegani, Ibrahim, Ikin, and Mourant (1950). This value was selected simply because it was intermediate between the value for the South African Bantu, 0.633 (Shapiro, 1951) and that for the Ewe of the Gold Coast, 0.593 (Armattoe, 1950). It may seem that the latter value, the only one available from West Africa at the time, ought to have been used in making the estimate; but the marked deviations from other African Negro values in the R^1 (*CDe*) and R^2 (*cDE*) values in Armattoe's data for the Ewe made us somewhat distrustful of his determinations (see Glass and Li, Table 3). We would have done well to use his R^o value, since it turns out to be almost exactly right.

In the present calculations there arises the problem of what to do with the D^u frequency. In serological testing D^u sometimes reacts as D, sometimes as d, depending on the antiserum used. Mourant (1954) proposes that D^u be reckoned as equivalent to d in series where no test for D^u was performed. But on the other hand, there is evidence that D^u has arisen chiefly, if not entirely, at the expense of D. Since it is not clear at what time in the past this has taken place and since the frequency of D^u varies considerably, from 0.00% to 11.27%, among the Nigerians, it might be better to base the estimate on the total of $D + D^u$. Unfortunately, there is at present no evidence regarding the frequency of D^u among the North American Negroes. Consequently the best that can be done is to make the estimate both ways, so as to set upper and lower limits to the estimate of gene flow based on R^o. It is also uncertain whether it would be better to assume that the slaves came mainly from the coastal areas of West Africa, from the interior, or from both equally. If D and D^u are combined, the total would not be sensibly different for Southern and Northern Nigeria; but if D^u is excluded the value for Southern Nigeria is higher than for Northern Nigeria (see Table 1). Again, if D and D^u are combined, the value for the Ashanti is higher and that for the Ewe is lower than the average for the four parts of Nigeria; but if D^u is excluded, the Ashanti value is slightly lower than the value for all Nigeria, and the Ewe value is very much below. It is clear that the values show much better agreement when D and D^u are totalled than when D is taken alone.

Another problem is how best to average the values for different areas when the samples are different in size. If the samples were drawn from a homogeneous population, then the average should be weighted according to the respective sizes of the contributory samples. Thus, in the previous study (Glass and Li, 1953) the samples of North American Negroes from New York City (2 series) and from Baltimore (1 series) did not prove to be significantly different from one another and the R^o frequency was therefore calculated by combining the three samples. In West Africa the tribes are clearly heterogeneous. Sample size must therefore be ignored unless it is proportional to population in each and every tribe. There being no assurance that this is the case, it seems better to treat each sampled tribe or area as a unit, adding the calculated frequencies for each sampled population and dividing by the number of such populations. Inasmuch as the sample size for the six available West African populations ranged only from 106 to 167, there is little error in considering them as equal. It would be far more important to know the actual provenience of the slaves taken to North America, but it seems impossible to do better than to sample as wide a range of populations from West Africa as possible, from Gambia in the north to Angola in the south (Herskovits, 1928, 1933, 1942). In time, the data to refine the present estimates should be available.

Certain other values in making the estimates have been altered. The R^o frequency for the U. S. Whites remains the same, for although several more series of Rh tests on U. S. Whites have been reported, none compare in extensiveness with the great series of Unger et al. (1946) and the other series are in reasonable agreement with it. Wiener has reported two series of New York City Whites, in one of which the R^o frequency was .0309 (N = 1468) and in the other .0260 (N = 743), and Levine

has reported one with a frequency of .0335 (N = 335). The average of all four series is .0284, not significantly different from the large series alone. The series of Minnesota Whites included by Matson et al. in the study of the Chippewa Indians seems to be so far out of line with other Whites, even from Scandinavia, whence many of the Minnesotans are derived, that it has seemed best to ignore them in these calculations.

In reexamining the data from the series of New York City Negroes published by Wiener, Belkin, and Sonn (1944), and comparing these with the data given in Table 21 of Mourant (1954), a source of considerable confusion was uncovered. Mourant cites Wiener, Sonn, and Belkin (1943), Wiener, Sonn, and Belkin (1944), and ibid., in three successive rows of the table. These might be taken as three independent samples of the U. S. Negro population. However, they are not so, for the two papers include essentially the same individuals, as the original papers state. The final report on these individuals is contained in Wiener, Belkin, and Sonn (1944), in which a footnote to Table 3 states that it includes, together with a few additional bloods, the data reported in Wiener, Sonn, and Belkin (1944). The final report, like the second paper which was used by Mourant, breaks up the data into two series, in which the numbers of individuals were respectively 94 and 137, or a total of 231, after excluding two cases of atypical reaction. Glass and Li (1953) used the frequencies of the Rh subtypes as cited by Potter (1947) from the final report. But Potter undertook to combine the two series, and in so doing recorded a wrong total; and thus all the frequencies she calculated were in error. From the report by Wiener, Belkin, and Sonn I have reestimated the gene frequencies and have applied Bernstein's correction, which the authors failed to do. The revised values are as follows: No., 231; R^1 (*CDe*), 0.1706; R^2 (*cDE*), 0.1618; R^o (*cDe*), 0.3589; r' (*Cde*), 0.0217; r'' (*cdE*), 0.0069. These revised values have been used in all the calculations of this paper in which reference is made to Wiener et al. (1944).

An additional U. S. Negro series is now available (Wiener, Gordon, and Cohen, 1952), with an R^o frequency of 0.4675 (N = 284). The series by Miller, Rosenfield, and Vogel (1951) has not been used because those authors state that they specifically selected subjects for darkness of skin. It is therefore not surprising that they found the highest R^o frequency of all, namely 0.4850. Such data cannot be used to characterize the whole U. S. Negro population, as socially defined.

Table 1 reveals that the reduction of the frequency of R^o from 0.630 to 0.600 (if D and D^u are combined) slightly reduces the previous estimate of the amount of white admixture in the North American Negro gene pool; and that if D alone is used the estimated admixture is reduced very considerably, being lowered from 30 per cent to 22 or 23 per cent. The estimated gene flow per generation is correspondingly reduced. The lower and upper limits of estimate are .0241 and .0336 per generation, rather than .0358 (Glass and Li, 1953).

There are three other genes the frequencies of which are approximately the same in the North American Indian and the U. S. White, and which can therefore be used to check the over-all admixture of foreign genes with the original heritage of the American slaves. These are S and the MS combination at the MNS locus, and the K/k alleles of the Kell blood groups. Table 2 demonstrates that the S allele in the

TABLE 1

ESTIMATION OF THE AMOUNT OF GENETIC ADMIXTURE IN AND GENE FLOW INTO THE NORTH AMERICAN NEGROES, CALCULATED FROM THE FREQUENCIES OF CHROMOSOME R^o (cDe)

W. African Negroes	$D + D^u$	D	*U. S. White*		*Amerindian*	
S. Nigeria (2)*	.6004	.5820	New York City (1)	.0279	Chippewa (1)	.0000
N. Nigeria (2)	.6090	.5532				
Nigeria (4)	.6047	.5676				
Ewe (1)	.5478	.4795				
Ashanti (1)	.6244	.5576				
W. Africa (6)	.5985	.5512				

U. S. Negroes	
Baltimore (1)	.4381
Average (4)	.4332

$$Admixture = 1.00 - \frac{q_h - Q}{q - Q}$$

	Lower estimate	*Higher estimate*
$D + D^u$	$1.00 - \frac{.4381 - .0279}{.5985 - .0279} = 28.1\%$	*or* $1.00 - \frac{.4332 - .0279}{.5985 - .0279} = 28.97\%$
D	$1.00 - \frac{.4381 - .0279}{.5512 - .0279} = 21.62\%$	*or* $1.00 - \frac{.4332 - .0279}{.5512 - .0279} = 22.55\%$

	Gene Flow	
	$D + D^u$	D
m =	.0325 or .0336	.0241 or .0252

Data from following sources: *Nigeria*, (SW – 145; SE – 106; Jos Plateau – 124; N – 165) Chalmers, Ikin, and Mourant, 1953 (M); *Ewe* (161), Armattoe, Ikin, and Mourant, 1953 (M); *Ashanti* (113), Armattoe, Ikin and Mourant, 1953 (M); *U. S. White* (7317), Unger, Weinberg, and Lefkon, 1946 (M); *Chippewa* (161), Matson, Koch, and Levine, 1954; *Baltimore Negroes* (907), Glass and Li, 1953 (M); *New York Negroes*, (135) Levine, 1945 (M); (231) Wiener et al., 1944; (284) Wiener and Gordon, 1952 (M). Chromosome frequencies are those calculated by Mourant (1954) by the method of maximum likelihood, or are averages derived from them by the methods described in the text. The numbers in parentheses given with the sources of data in this and the following tables are the numbers of individuals in the respective series. [M, Mourant, 1954]

* In this and the following tables the numbers in parentheses are the numbers of separate series used in the respective estimates.

aggregate ($MS + NS$) yields an estimate of 17.92% of admixture; but when the MS combination alone is used, the admixture is found to be only 4.9%. The latter value is so far below all other estimates that we may be sure it is unreliable, and this throws doubt on the estimate based on S as well. It is not difficult to determine the sources of unreliability here. Of the two available series of tests reporting the distribution of MNS in the North American Negroes, the larger is that compiled by Miller, Rosenfield, and Vogel (1951), which must unfortunately be discarded for the present purposes, for the reason already given. The remaining series (Neel and

TABLE 2

AMOUNT OF GENETIC ADMIXTURE IN THE NORTH AMERICAN NEGRO CALCULATED FROM THE FREQUENCIES OF THE S AND MS BLOOD GROUP GENES

S

W. African Negro			*U. S. White*		*Amerindian*	
S. Nigeria	(2)	.1176				
N. Nigeria	(2)	.1512				
Nigeria	(4)	.1344	New York (1)	.3374	Chippewa (1)	.3416

*Expectancy:** $D + D^u$ .1915–.1933
D .1783–.1802

*Observed:**
U. S. Negroes (1) .1708

Admixture: 17.92%

MS

W. African Negro			*U. S. White*		*Amerindian*	
S. Nigeria	(2)	.0803				
N. Nigeria	(2)	.0899				
Nigeria	(4)	.0851	New York (1)	.2524	Chippewa (1)	.2829

*Expectancy:** $D + D^u$ .1320–.1336
D .1213–.1229

*Observed:**
U. S. Negro (1) .0933

Admixture: 4.9%

Data from following sources: *Nigeria* (451), Chalmers, Ikin, and Mourant, 1953 (M); *U. S. White* (394), Wiener, Di Diego, and Sokol, 1953 (M); *Chippewa* (161), Matson, Koch, and Levine, 1954; *U. S. Negroes*, Mich. (96), Neel and Hanig, 1951 (M). [M, Mourant, 1954]

* This and the following tables are so arranged that the respective positions of the expectancies and observed (U. S. Negro) values indicate roughly their relative positions on a scale delimited by the gene frequencies in the W. African Negro and U. S. White. Thus it can be seen at a glance from the present table that the observed frequencies do not depart from those of the W. African Negro quite as much as would be expected on the basis of the R^o frequencies.

Hanig, 1951) numbers only 96 individuals, so that the experimental error is high. The only available U. S. Negro series for the Kell antigens is that of Miller et al., so that for the present we must forego its use. In any case, the range between the frequency in West African Negroes (.0000–.0088, 2 series) and the frequencies of U. S. Whites (.0599, 2 series) and American Indians (.0776, Chippewas) is at the lower limit of usefulness.

For purposes of comparing the amounts of admixture calculated from different gene frequencies, an expectancy for the frequency in the U.S. Negro is calculated in each case from the R^o data. This is done by multiplying the difference between the frequencies in the West African Negroes and the U. S. Whites by the amount of admixture calculated for the R^o gene (28.1% − 27.4% for $D + D^u$; 21.6% − 20.8%

TABLE 3

THE KIDD (Jk^a) BLOOD GROUP FREQUENCIES

W. African Negro	*Amerindian*		*U. S. White*
Nigeria (1) .783	Blood (1) Obs. .722		(2) .518
	Corr. .770		
Expectancy: $D + D^u$		.709–.706	
D		.726–.723	
Observed:			
U. S. Negro—New York (1)	.7315		
Admixture: 19.4%			

Sources of data: W. Africans (85), Ikin and Mourant, 1952; *Blood* (194), Chown and Lewis, 1953 (M); *U. S. White* (Boston, 189), Allen, Diamond, and Niedzula, 1951 (M); (New York, 726), Rosenfield, Vogel, Gibbel, Ohno, and Haber, 1953 (M); *U. S. Negro* (New York, 305), Rosenfield et al. 1953 (M). [M, Mourant, 1954]

for D). For example, for S, one finds .3374 − .1344 = .2030. 28.1% of this = .0571, which added to .1344 gives .1915, the upper limit of the expectancy if the parameter $D + D^u$ is used.

A situation analogous to that in which the U. S. White and Indian frequencies are alike is that wherein the gene frequencies in the American Indian and the West African Negro populations are nearly identical, whereas the frequency in the U. S. White population is quite different. In this situation, too, no genetic introgression from the American Indian into the U. S. Negro population would be detectable, and all the difference between the West African and U. S. Negro populations would be attributable to admixture with the White population. This relationship is exemplified by the Kidd blood group alleles, Jk^a/Jk^b (Table 3). No data for the Chippewas are available for the Kidd antigens, but Chown and Lewis (1953) have reported series of tests of the Blood and Blackfoot Indians. The former series included 194 individuals. Chown and Lewis, on the basis of the assumed absence of B and cde from pure Indians and the frequency of these genes in the Bloods, estimated that approximately one-sixth of the present genes in the tribe are of White origin; and thus arrived at an estimate of .77 for the gene frequency of Jk^a. But there is in any case a very strong objection to using data from the Blood and Blackfoot tribes in such studies as the present one. The Blood and Blackfoot are among the American Indian tribes possessing the highest known frequencies in the world of A (.64), and in this respect they depart radically from the more eastern Indian tribes, whose frequency of A (see Snyder, 1926) is low and ranges from a maximum of .151 down to .035. For example, the Bloods are markedly different in their frequency of A from the Chippewas (.088). Consequently, until something is known of the frequency of the Kidd alleles in other American Indian tribes, the comparison with the Bloods may be entirely misleading. The data for Africans reported by Ikin and Mourant (1953) include, among 120 tested individuals, 20 who were from Kenya (Luo). These have been subtracted so as to give a purely Nigerian (Jos Plateau and S. Nigerian) sample. The data for the U. S. Negro are those of Rosenfield, Vogel, Gibbel, Ohno, and Haber

(1953). As in apparently all of the studies by Rosenfield and his collaborators on the U. S. Negroes, individuals were selected for their dark skin color. These data therefore fail to provide suitable material for studying the degree of foreign admixture in the total U. S. Negro population. At the same time, as Table 3 clearly shows, the amount of admixture in these selected individuals is very considerable and in fact approaches very closely the amount predicted from the R^o frequencies when D alone is used for the estimation and D^u is excluded from consideration. From general genetic considerations, this agreement is what would be expected unless certain genes for dark skin color were very closely linked with the particular blood group loci being studied and the racial intermixture had been limited to a couple of generations. Otherwise segregation and recombination of loci would occur, and the selection of individuals on the basis of one genetic trait would not afford a good index to their "racial purity" in respect to other genetic traits. However, if the skin color differences between Negroes and Whites rest, as Stern (1953) has estimated, upon 4 to 6 loci, then linkage could have a small, if not precisely calculable, effect upon the blood group frequencies. Moreover, the U. S. Negro is assuredly not a panmictic population, but a heterogeneous population with real differences in frequency of admixture. Consequently, the darker an individual's skin color the greater the chance that the rest of his genotype approximates the original West African constitution. Such appears to be shown by the fact that in most instances the data for the U. S. Negro gathered by Rosenfield and his coworkers (see Miller, Rosenfield, and Vogel, 1951) yield frequencies somewhat closer to those of the West African Negro than do the other, more randomly sampled, series of data for the U. S. Negro. It is indeed difficult to see what group the Negroes in the series of Rosenfield et al. represent, except themselves alone. They clearly do not represent either the West African Negroes or the generality of U. S. Negroes.

CASES WHEREIN THE ENTIRE SHIFT IN GENE FREQUENCY WOULD BE ATTRIBUTABLE TO GENETIC ADMIXTURE OF AMERINDIANS AND NEGROES

In certain cases the allelic frequencies in the West African Negroes and the North American Whites are identical or exceedingly similar. Whenever that is the case, and whenever at the same time the allelic frequency in the North American Indians is quite different, any significant observed difference between the West African Negroes and the North American Negroes must be attributable wholly to non-White, i.e., to Amerindian, admixture. Two blood group genes fall into this category, namely, O of the ABO blood group system and M of the MN blood group system. In the former instance, the American Indian exceeds the West African Negro by 23.18% and in the latter instance by 34.2%.

For the ABO blood groups there are, in addition to the recent data for the Chippewa, two other available series in which an effort was made to separate pure from mixed Indians. These series are those for the Cherokees (Snyder, 1926) and Sioux (Matson and Schrader, 1933). It should be noted that the Cherokee series has not been entered as such in Boyd's compilation of blood group data (1939); for Boyd entered only the values for the entire series, of 250 individuals, mixed and pure

combined. However, Snyder stated in the text of his paper that 110 of the 250 were known from "records and the personal knowledge of the physician" to be pure and that, among these, 93.6 per cent were of Group I (O), whereas among those known to be mixed the proportion was 59.3 per cent. Unfortunately, the frequencies of groups A and B among the 110 pure Cherokees were not given. The data on the Sioux, from Matson and Schrader, are equally valuable for the present purpose, because the Sioux and Cherokees—particularly the latter—represent much better than the Chippewas the Indian tribes which may have had an opportunity to intermix in some degree with the North American Negroes. For the Sioux, fortunately, the frequencies of all the ABO groups are given. It is important, in considering the validity of the use in the present study of the Chippewas to represent the American Indians with whom the Negroes might have interbred, that Chippewas, Cherokees, and Sioux, all three, agree extremely closely in all of those comparisons which can be made between them in these limited data.

Table 4 demonstrates that in neither of these exceptionally favorable cases for detecting the introgression of an American Indian element into the U. S. Negro is there any sign of a significant admixture.

CASES WHEREIN BOTH WHITE AND AMERINDIAN GENE FREQUENCIES DEPART FROM THE WEST AFRICAN IN THE SAME DIRECTION, BUT THE AMERINDIAN TO A SMALLER DEGREE

When this situation obtains, the effect of any significant amount of gene flow from the American Indian into the U. S. Negro population would tend to reduce the divergence of the latter from the West African frequencies below the expectancy calculated upon the assumption that all significant admixture of U. S. Negroes was with the U. S. White population. This may be termed a case of "supplementary action, diminished by Amerindian effect." Two cases of this relationship exist, R^1 of the Rh alleles and P. In the former the difference between the frequencies in the W. African Negro and the U. S. White is 35.11%, between the Amerindian and White 8.36%. Thus the working range is large, but the difference to be expected in the event of even a very large Amerindian admixture would be slight. As for P, the difference between the frequencies in the U. S. White and W. African Negro is 23.83%, but between the American Indian and White only 6.49%; so that the minimizing effect to be expected in case there is any significant American Indian admixture would be even less apparent than in the instance of the R^1 frequencies.

Table 5 presents the analysis of the available data. Clearly there is no evidence of any significant amount of Indian admixture in the R^1 frequencies, if the expectancy is based on D alone; and even if based on $D + D^u$, the diminution in the observed frequency is less than 1 per cent, which must be considerably below the limit of experimental error.

In regard to P, an anomalous situation exists, for the mean frequency reported in the N. American Negroes is actually greater than the frequency reported in the W. African Negroes, although it would be expected, on the basis of all the other evidence as to the amount of genetic modification of the N. American Negro, to be less. [In

TABLE 4

COMPARISONS OF GENE FREQUENCIES IN CASES WHEREIN THE W. AFRICAN NEGRO AND U. S. WHITE FREQUENCIES ARE NEARLY IDENTICAL AND THE N. AMERICAN INDIAN FREQUENCY IS QUITE DIFFERENT

O

W. African Negro		*U. S. White*		*Amerindian*	
Nigeria (4)	.730	New York City (1)	.674	Chippewa (1)	.936
				Cherokee (1)	.9675
Other W. African (5)	.673	N. Car.? (1)		Sioux (1)	.947
Average (9)	.704			Aver. (3)	.950

Expectancy

$D + D^n$	.696–.695
D	.698–.697

Observed

U. S. Negro (3) .679

M

W. African Negro		*U. S. White*		*Amerindian*	
Ewe (2)	.568	New York City (3)	.540	Chippewa (1)	.718
Ashanti (1)	.438				
Nigeria (4)	.460				
W. Africa (6)	.476				

Expectancy

$D + D^n$	.494–.495
D	.490

Observed

U. S. Negro (5) .489

Sources of data:

O. W. African Negro: (2251) Yoruba, Sierra Leone, Fr. Guinea, Senegal, Ewe (B; G and L); Nigeria (542), Chalmers, et al., 1953 (M). *U. S. White:* New York (10,000), Tiber (B; G and L); N. Car.? (20,000) Snyder (B; G and L). *Amer. Indian:* Chippewa (161), Matson, et al., 1954; Cherokee (110), Snyder, 1926; Sioux (48), Matson and Schrader, (B). *U. S. Negro:* Baltimore (605), Glass and Li, 1953; N. Car.? (500), Snyder (B; G and L); New York City (730), Landsteiner and Levine (B; G and L).

M. W. African Negro: Ewe (853), Armattoe, 1951 (M); Ewe (161), Armattoe et al., 1953 (M); Ashanti (113), Armattoe et al., 1953 (M); Nigeria (500) Chalmers et al., 1953 (M). *U. S. White:* Combined (6129), Wiener, 1943; New York City (582), Wiener et al., 1944 (M); New York City (954), Wiener, et al., 1953 (M). *Amer. Indian:* Chippewa (161), Matson et al., 1954. *U. S. Negro:* Baltimore (580), Glass and Li (M); New York City, combined (278), Wiener, 1943 (M); New York (227) Wiener et al., 1945 (M); Michigan (96), Neel and Hanig, 1951 (M). [B, Boyd, 1939; G and L, Glass and Li, 1953; M, Mourant, 1954]

only one series has a lower value than that in the W. African Negroes been reported, and that, strangely enough, in one of the studies by Miller et al. (cited from Mourant, 1954) in which presumably the group was selected for dark skin color. The two series by Miller et al. have been excluded from the tabulation, but would not modify the

TABLE 5

COMPARISONS OF GENE FREQUENCIES IN CASES WHEREIN THE SERIATION IS W. AFRICAN NEGRO, N. AMERICAN INDIAN, AND U. S. WHITE

(Supplementary Action, Diminished by Amerindian Effect)

R^1

W. African Negro		*Amerindian*		*U. S. White*	
Ewe (1)	.0858	Chippewa (1)	.3367	New York City (3)	.4203
Ashanti (1)	.1195				
Nigeria (4)	.0500				
Average (6)	.0692				

Expectancy:

$D + D^a$	.1675–.1705
D	.145–.148

Observed:

U. S. Negro (3) .1582

P

W. African Negro		*Amerindian*		*U. S. White*	
Nigeria (2)	.7803	Chippewa	.6069	New York City (2)	.5225
				Minnesota (1)	.5745
				Aver. (3)	.5420

Expectancy:

$D + D^a$	.713–.712
D	.728–.726

Observed:

U. S. Negro (2) .847(!)

Sources of data:

R^1. *W. African Negro:* Ewe (161), Armattoe et al., 1953 (M); Ashanti (113), Armattoe et al., 1953 (M); Nigeria (540), Chalmers et al., 1953 (M); *Amer. Indian:* Chippewa (161), Matson et al., 1954. *U. S. White:* New York City (7317), Unger et al., 1946 (M); N.Y.C. (1071), Wiener and Gordon, 1949 (M); N.Y.C. (1468), Wiener et al., 1945 (M). *U. S. Negro:* N.Y.C. (231), Wiener et al., 1944; N.Y.C. (135) Levine, 1945 (G and L; M); Baltimore (907), Glass and Li, 1953 (M).

P. *W. African Negro:* Nigeria (114), Barnicot and Lawler, 1953 (M); Nigeria (29), Chalmers et al., 1953 (M). *Amer. Indian:* Chippewa (161), Matson et al., 1954. *U. S. White:* N.Y.C. (265), Landsteiner and Levine, 1929 (M); N.Y.C. (237), Wiener and Unger, 1944 (M); Minnesota (300), Matson et al., 1954. *U. S. Negro:* N.Y.C. (267), Landsteiner and Levine, 1929 (M); N.Y.C. (73), Wiener and Unger, 1944 (M). [M, Mourant, 1954]

conclusions if averaged in.] Consequently, the values reported for the frequencies of *P* must be regarded as unreliable in some or all series, and cannot be used in answering the present problem. It is indeed well known among serological workers (Levine, pers. commun.) that antisera for *P* are quite variable and that reliable comparisons between different groups of individuals cannot be made unless all of them were typed with the same antiserum.

CASES WHEREIN BOTH WHITE AND AMERINDIAN GENE FREQUENCIES DEPART FROM THE WEST AFRICAN IN THE SAME DIRECTION, BUT THE AMERINDIAN TO A GREATER DEGREE

In this situation, the effect of a significant amount of gene flow from the American Indian into the N. American Negro population would tend to increase the divergence of the latter from the West African frequencies so as to attain values greater than the expectancies calculated upon the assumption of gene flow into the Negro population from the U. S. White population alone. This might be called "supplementary action, enhanced by Amerindian effect."

Three genes, *B* of the ABO system, R^2 of the Rh system, and *Ns* of the MNS system, exhibit this relationship. In the case of *B*, the difference in gene frequency between the highest and lowest of the three base populations, the West African and the N. American Indian, is quite small, being only 15.13%. The U. S. White frequency is, however, almost exactly intermediate between the W. African and the American Indian, so that if the genetic introgression from the Indian population into the U. S. Negro population has been considerable, it might be detected. R^2 presents a highly favorable case for casting light on the present problem. The difference between W. Africans and Indians amounts to 44.42%, and the frequency in the U. S. Whites differs only by 6.4% from that in the West Africans. Consequently even a small genetic introgression from the American Indian into the U. S. Negro might be expected to raise the observed R^2 frequency above the expectancy calculated on the basis of White admixture alone.

Ns, like *MS*, yields anomalous results. Whereas the amount of genetic admixture calculated from *MS* is only 4.9% (Table 2), it is 60.6% for *Ns*, if it be assumed that all admixture was with Whites, and 49.2% if all admixture was with Indians. In other words, for some reason the *MS* combination is more frequent and the *Ns* combination less frequent than would be expected.

Table 6 presents the analysis based on *B*, R^2, and *Ns*. Clearly if *Ns* is excluded as being anomalous, there is again no indication of any detectable shift in gene frequencies attributable to American Indian admixture.

CASES WHEREIN WHITE AND AMERINDIAN GENE FREQUENCIES DEPART FROM THE WEST AFRICAN IN OPPOSITE DIRECTIONS

The final group of cases comprises those which might be denominated cases of "competitive" or "opposed" action, because in them the influence of any genetic admixture between the American Negro and Indian populations would have the effect of reducing the shift from the original W. African frequencies toward those of the U. S. White population. Into this category fall *A* of the ABO system, *r* of the Rh system, and *MS* of the MNS system.

In the case of *A*, the gene frequency in the U. S. White population is 10.0% greater than in the W. African Negroes, and the gene frequency in the N. American Indians is 8.7% lower than that in the W. African Negroes. Although the range of differences is not great, the symmetry is such that any pronounced admixture of the American

TABLE 6

COMPARISONS OF GENE FREQUENCIES IN CASES WHEREIN THE SERIATION IS W. AFRICAN NEGRO, U. S. WHITE, AND N. AMERICAN INDIAN

(Supplementary Action, Enhanced by Amerindian Effect)

R^3

W. African Negro		*U. S. White*		*Amerindian*	
Ewe (1)	.0528	New York City (3)	.1499	Chippewa (1)	.5303
Ashanti (1)	.0265				
Nigeria (4)	.1093				
W. Africa (6)	.0861				

Expectancy:

$D + D^n$	.1040–.1045
D	.0999–.1005

Observed:

U. S. Negro (4) .1088

B

W. African Negro		*U. S. White*			*Amerindian*	
Nigeria (4)	.1278	New York City (1)	.078		Chippewa (1)	.000
Other W. African (5)	.174	N. Car. (?) (1)			Sioux (1)	.000
Average (9)	.1513				Aver. (2)	.000

Expectancy:

$D + D^n$	.1307–.1301
D	.1355–.1348

Observed:

U. S. Negro (3) .139

Ns

W. African Negro		*U. S. White*		*Amerindian*	
Nigeria (4)	.4901	New York City (1)	.3529	Chippewa (1)	.2208

Expectancy:

$D + D^n$	.4515–.4503
D	.4605–.4591

Observed:

U. S. Negro (1) .4068

Sources of data:

R^3. *W. African Negro:* Ewe (161), Armattoe et al., 1953 (M); Ashanti (113), Armattoe et al., 1953 (M); Nigeria (540), Chalmers et al., 1953 (M). *U. S. White:* N.Y.C. (7317) Unger et al., 1946 (M); N.Y.C. (1468) Wiener et al., 1945 (M); N.Y.C. (1071), Wiener and Gordon, 1949 (M). *Amer. Indian:* Chippewa (161), Matson et al., 1954. *U. S. Negro:* Baltimore (907), Glass and Li (M); N.Y.C. (135), Levine, 1945 (M); N.Y.C. (231), Wiener et al., 1944; N.Y.C. (284), Wiener et al., 1952 (M).

B. *W. African Negro:* (2251) Yoruba, Sierra Leone, Fr. Guinea, Senegal, Ewe (G and L); Nigeria (542), Chalmers et al., 1953 (M). *U. S. White:* N.Y.C. (10,000), Tiber (G and L); N. Car.-? (20,000), Snyder (G and L). *Amer. Indian:* Chippewa (161), Matson et al., 1954; Sioux (48), Matson and Schrader (B). *U. S. Negro:* Baltimore (605), Glass and Li, 1953; N. Car. (500), Snyder (G and L; B); N.Y.C. (730), Landsteiner and Levine (G and L; B).

Ns. *W. African Negro:* Nigeria (451), Chalmers et al., 1953 (M). *U. S. White:* N.Y.C. (394), Wiener et al., 1953 (M). *Amer. Indian:* Chippewa (161), Matson et al., 1954. *U. S. Negro:* Mich. (96), Neel and Hanig, 1951 (M). [B, Boyd, 1939; G and L, Glass and Li, 1953; M, Mourant, 1954]

TABLE 7

COMPARISON OF GENE FREQUENCIES IN CASES WHEREIN THE SERIATION IS U. S. WHITE, W. AFRICAN NEGRO, AND N. AMERICAN INDIAN—OPPOSITIONAL CASES

A

U. S. White		*W. African Negro*		*Amerindian*	
New York City (1)	.248	W. Africa (5)	.153	Chippewa (1)	.0642
N. Car. ? (1)		Nigeria (4)	.1423		
		W. Africa (9)	.1484		

Expectancy:

$D_4^3 + D^a$	.1769–.1754
D	.1708–.1699

Observed:

U. S. Negro (3) .1875

r

U. S. White		*W. African Negro*		*Amerindian*	
New York City (2)	.3842	Nigeria (4)	.2005	Chippewa (1)	.0000
		Ewe (1)	.2348		
		Ashanti (1)	.2296		
		W. Africa (6)	.2111		

Expectancy:

$D + D^a$	.2612–.2597
D	.2502–.2485

Observed:

U. S. Negro (4) .2637

Ms

U. S. White		*W. African Negro*		*Amerindian*	
New York City (1)	.3098	Nigeria (4)	.3755	Chippewa (1)	.4376

Expectancy:

$D + D^a$	.3564–.3570
D	.3607–.3613

Observed:

U. S. Negro (1) .4068

Sources of data:

A. *U. S. White:* N.Y.C. (10,000), Tiber (B; G and L); N. Car.? (20,000), Snyder (B; G and L). *W. African Negro:* (2251) Yoruba, Sierra Leone, Fr. Guinea, Senegal, Ewe (G and L); Nigeria (542), Chalmers et al., 1953 (M). *Amer. Indian:* Chippewa (161), Matson et al., 1954. *U. S. Negro:* Baltimore (605), Glass and Li, 1953; N. Car. (500), Snyder (B; G and L); N.Y.C. (730), Landsteiner and Levine (B; G and L).

r. *U. S. White:* N.Y.C. (7317), Unger et al., 1946 (M); N.Y.C. (1071), Wiener and Gordon, 1949 (M). *W. African Negro:* Nigeria (540), Chalmers et al., 1953 (M); Ewe (161), Armattoe et al., 1953 (M); Ashanti (113), Armattoe et al., 1953 (M). *Amer. Indian:* Chippewa (161), Matson et al., 1954. *U. S. Negro:* Baltimore (907), Glass and Li, 1953 (M); N.Y.C. (231), Wiener et al., 1944; N.Y.C. (135), Levine, 1945 (M); N.Y.C. (284), Wiener et al., 1952 (M).

Ms. *U. S. White:* N.Y.C. (394), Wiener et al., 1953 (M). *W. African Negro:* Nigeria (451), Chalmers et al., 1953 (M). *Amer. Indian:* Chippewa (161), Matson et al., 1954. *U. S. Negro:* Mich. (96), Neel and Hanig, 1951 (M). [B, Boyd, 1939; G and L, Glass and Li, 1953; M, Mourant, 1954]

Indian should be apparent. It is significant that this is another of the few cases in which there are data for "pure" Indians of other tribes than the Chippewa.

In the case of *r*, the range is much greater than for *A*, the difference in gene frequency between U. S. White and W. African Negro being 17.1% and between W. African Negro and Amerindian being 21.1%. Once again, the symmetrical distribution of these differences around the W. African Negro frequency, in the middle, makes the data of particular value in answering our question.

Table 7 reveals that neither the *A* frequencies nor the *r* frequencies yield the slightest indication of any effect of Amerindian admixture.

Ms, like the preceding MNS examples, behaves anomalously. At first sight it might seem that this similarity could rest upon a general excess of *s* and deficiency of *S* in relation to expectation, as shown to exist in Table 2. Actually, the situation is more involved than this, for Table 6 indicates that there is a deficiency of *Ns*, which is offset by the excess over expectation of the *Ms* shown in Table 7. No explanation can be advanced for these anomalies at the present time; but it may be pointed out that the data of Miller et al., although excluded from the present computation for the reason previously given, agree with the data of Neel and Hanig very closely. Here is evidently a puzzling situation which only the further study of MNS frequencies in the respective populations can resolve.

DISCUSSION

The answer to the question whether there is any genetic evidence of a significant amount of gene flow from the Amerindian into the U. S. Negro population is clearly in the negative. Excluding the dubious *S-s* frequencies, the *A*, *B*, *O*, R^1, R^2, *r*, and *MN* frequencies alike indicate no significant shifts in the respective directions to be expected if admixture with the N. American Indian had been considerable. The *A* and *r* cases are particularly conclusive, because in both those cases the effects of the admixture of White and Indian genes would be vectorially opposed to one another, and the range of differences in gene frequency is very great (25% and 38% respectively).

It should not be concluded, of course, that the result of this analysis means that no Indian genes have entered the N. American Negro gene pool. It means only that the effect must be regarded as of very minor magnitude, probably not over the present limits of experimental error in determining gene frequencies in the respective populations. Nor ought one to conclude that because the Negro gene pool has relatively few American Indian genes, the converse is likewise true. That would by no means follow; for the American Indian populations being so much smaller and the tribes so much more isolated in mating than the American Negro population, it may well be that in certain Indian tribes the proportion of genes derived from Negroes is considerable. In fact, the conclusions reached in the present analysis merely reflect what a judgment *a priori* might have decided. For escaped Negro slaves in colonial times would have left descendants among any Indian tribes with whom they took refuge and intermarried; but those descendants would have remained in the socially defined "Indian" population for the most part. In order that genes from the American Indian population might enter the Negro gene pool, such hybrid individuals would

have to forsake their Indian homes and relatives, migrate into some Negro community, and there become accepted as "Negro." It seems far less likely that Indian braves would have mated with Negro women who remained within the Negro community than that admixture was mainly through Negro males who escaped from slavery and found refuge among the Indians. Consequently the Indians were far more exposed to introgression of Negro genes than were Negroes to the introgression of Indian genes.

Why, then, have the anthropologists and sociologists, following Herskovits and Meier, generally assumed that the U. S. Negro has so considerable an admixture of genes from the North American Indians? It seems very probable that the misconception is due to a failure to appreciate the necessary consequences of the Mendelian, that is, particulate, nature of heredity. An Indian ancestor, four or five generations removed, might indeed have a large number of descendants at the present day. It is not so immediately apparent that his contribution to the Negro gene pool is limited quantitatively to that initial set of genes present in each one of his functioning gametes that produced a hybrid offspring. Because of the Mendelian mechanism, the genes in each such original gamete simply become distributed more and more widely among the descendants. In a stable population no introduced gene would increase in number, except by chance or the effects of natural selection, since an F_1 hybrid, or heterozygote, is by the rules of probability expected to produce, among every two offspring, only one carrier of the gene, and like the parent a heterozygote. In a population increasing in size the proportion of the introduced genes to the native genes would remain the same, as long as the reproductive fertility of the hybrid and nonhybrid individuals was the same. For example, if the population in the first generation subsequent to hybridization consisted of 100,000 persons, among whom 10 were hybrids, the net contribution of foreign genes to the gene pool is simply 0.005%, no matter how many individuals might eventually, generations later, be descended from the 10 hybrids. Consequently, unless the introduction of genes from the Indian population took place when the Negro population was very small, or unless the actual number of F_1 hybrids at some later date formed a significant portion of the population, say above 1.0%, and this was repeated over several generations, the contribution of the American Indians to the U. S. Negro gene pool would be too small to detect in the presence of the experimental and statistical errors of several per cent now incurred in our determinations of blood group frequencies.

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SUMMARY

1. Recent data published on the frequencies of various blood groups among the West African Negroes make it possible to revise the original estimates made by Glass and Li (1953) of the amount of foreign admixture now present in the U. S. Negro

population, and of the average amount of gene flow per generation required to account for it. The frequency of R^o (*cDe*) being taken as .5985 ($D + D^u$) or .5512 (D alone), the new estimate of the amount of admixture in the U. S. Negro population is 28.1–28.97% (based on $D + D^u$) or 21.62–22.55% (based on D alone). The revised estimates of the gene flow per generation are respectively .0325–.0336 or .0241 – .0252.

2. By calculating expectancies based on the frequencies of R^o, and upon the assumption that all foreign admixture with the U. S. Negroes was derived from the White population, it has proved possible to test the hypothesis that there has been a significant American Indian contribution to the U. S. Negro gene pool. The data for *A*, *B*, *O*, R^1, R^2, *r*, and *MN* agree in denying the hypothesis. The data derived from the *A* and *r* frequencies are particularly conclusive.

3. Anomalies in the available data for *P* and for *S* (MNS system) are pointed out. These anomalies made it necessary to exclude them from use in the present considerations.

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Concentration of Gastric Carcinoma, Peptic Ulcer, and Cholecystitis in a Family Group[1, 2]

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INTRODUCTION

FAMILY HISTORIES which have an unusually high percentage of the members affected with cancer, when compared with the presence of this disease in the general population, are often designated as "cancer families." A few cancer families have been reported which show concentration of cancer in the gastrointestinal tract (Hauser and Weller, 1936; Gardner and Stephens, 1950; Woolf and Gardner, 1950; Gardner and Woolf, 1952). These families give presumptive evidence for the localization of cancer of the gastrointestinal tract and point up the significance of genetic factors in these family groups.

Genetic factors also appear concerned in the development of peptic ulcers (Doll and Buch, 1950) although the mode of inheritance is still not clear. It has been difficult to separate gastric and duodenal ulcers in familial studies and to evaluate the interaction of heredity and environment. However, Doll and Kellock (1951) reported from a familial study of gastric and duodenal ulcer a strong tendency for an affected relation of a patient with an ulcer to have the ulcer in the same site.

Korner (1937) found that the frequency of cholecystitis among relatives of probands with gallbladder disease was over five times as great as among relatives of control probands who did not have gallbladder trouble. Huddy (1925) and Marcuse (1929) reported pedigrees with a high incidence of cholecystitis and cholelithiasis.

HISTORY OF THE FAMILY GROUP

From 1949 to 1953 family histories were collected for a familial study of gastric carcinoma. A physician, who referred us to probands for this study, called attention to a patient who had come to him for a gastrointestinal examination. This patient did not have cancer but went to the doctor because several members of her family had died of gastric cancer.

A personal interview was taken with the proband who was a 38 year old white woman of Polish descent. In an investigation of the family history which she and her relatives have given, an unusual concentration of cancer, particularly gastric cancer, peptic ulcer, and cholecystitis has been found.

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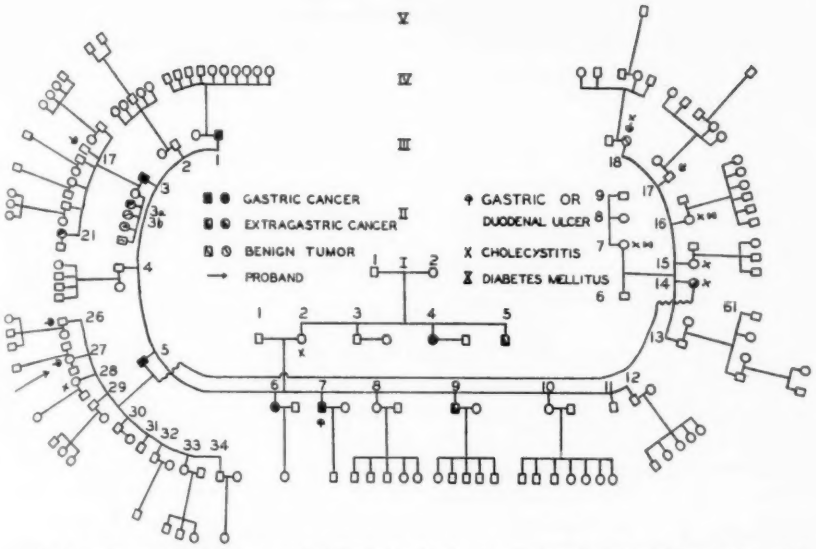

FIG. 1. Pedigree of the kindred studied. Individuals who are numbered are placed from right to left in order of birth in each sibship.

Only the proband lives in Texas and the other living relatives are widely scattered, so that we have not been able to contact other members personally. However, supplemental information has been gained by corresponding with the relatives. Data reported to us have been verified as far as possible from our present information by correspondence with physicians, hospitals, and bureaus of vital statistics which supplied clinical or pathological diagnoses on affected members in the history. In a few cases verifications still need to be obtained.

The history, as it is now known to us, is diagrammed in figure 1. Concentric rings represent generations and individuals who are numbered are placed from right to left in order of birth in each sibship. The proband, IV-27, is indicated by an arrow on the diagram.

Five generations are now included in the family history. The paternal relatives have been traced to the proband's great grandfather, who is listed in figure 1 as I-1. This man was born in Poland in 1816 and immigrated in later years to Minnesota. He died in 1909 at 92 years of age; the death certificate lists the cause as "organic heart paralysis."

Data on the paternal great grandmother, I-2, are unknown by the members of the family. She died before 1909 and no death certificate is available for additional information.

The paternal grandfather, II-1, was born in Germany in 1840, and came to Minnesota where he lived until the age of 90 years. During his life, he enjoyed good health. The cause of his death as stated on the death certificate was senile pneumonia and senile debility.

His wife, the proband's paternal grandmother, II-2, was born in Poland in 1846 and died in Minnesota in 1911 at the age of 64 years from a gallstone attack and renal calculi. Additional data given by the death certificate are that she developed gallstones about twenty years previous to death and renal calculi three years prior to death.

The paternal grandmother had three sibs, II-3, II-4, and II-5. The paternal greatuncle, II-3, died in 1916 at 55 years of age from a cerebral hemorrhage and fatty degeneration of the heart. A paternal greataunt, II-4, is reported to have died from cancer of the stomach at about 65 years of age. Sufficient data have not been obtained to confirm this condition. Another paternal greatuncle, II-5, died in 1948 at the age of 84 years from carcinoma of the prostate gland. Death certificates have been located for II-3 and II-5.

II-1 and II-2 had twelve children, nine boys and three girls.

III-1, a paternal uncle, died in 1922, aged 54 years, from carcinoma of the stomach which was diagnosed one year previous to death.

III-2, a paternal uncle, died in 1914, aged 45 years, of pulmonary tuberculosis which he developed at the age of 40 years.

III-3, a paternal uncle, died in 1937, aged 64 years, of carcinoma of the pylorus which was noted eight months prior to death and metastasized to the lungs one month before death.

III-4, a paternal uncle, died in 1920, aged 44 years, from injuries sustained in an automobile accident.

III-5, father of the proband, died in 1934, aged 57 years, of inoperable carcinoma of the stomach which began about one year prior to death.

III-6, a paternal aunt, died in 1923, aged 45 years, from a perforated gastric cancer and peritonitis.

III-7, a paternal uncle, died in 1930, aged 49 years, from carcinoma of the stomach which began one year prior to death. The death certificate also stated that the original lesion was a stomach ulcer which began five years previous to death (age 44).

III-8, a paternal aunt, was 70 years old at the time of the interview and had enjoyed good health.

III-9, a paternal uncle, died in 1949, aged 66 years, from carcinoma of the prostate gland which began ten months or more previous to death. This relative was hospitalized before death and clinical examination revealed extension into the periprostatic tissue and lung metastases.

III-10, a paternal aunt, died in 1948, aged 60 years, from coronary thrombosis. No other illnesses are known for this relative.

III-11, a paternal uncle, died in 1920, aged 29 years, from pneumonia. He was never married and no other illnesses are known.

III-12, a paternal uncle, was 62 years old at the time of interview of the proband. He is reported to be in good health.

The causes of death in this sibship have all been verified by death certificates. However, only two relatives, III-5 and III-9, were hospitalized, and then only received palliative treatment for advanced cancer. Therefore, it has not been possible to obtain pathological diagnoses on these conditions.

One case of cancer has been reported in the paternal cousins of the proband. Information was given by IV-17, who reported that his sister, IV-21, died in 1950, aged 35 years, of cancer of the lower intestine which she developed one year before death. This woman did not have surgery and as yet it has not been possible to locate the death certificate. Two maternal aunts of IV-21 have had neoplastic conditions. One, III-3a, developed carcinoma of the right breast in 1940 and died of metastatic carcinoma in 1942, aged 60 years. Her sister, III-3b, was treated in 1948 for a breast tumor and in 1949 for a stomach tumor. The pathological nature of the conditions of III-3b has not been obtained, but this individual is now living and well.

It has not been possible to investigate thoroughly other paternal cousin sibships of the proband. No additional cases of cancer are known by other relatives in the family.

One case of cancer and one benign tumor have occurred on the maternal side of the proband's family. III-14, the mother of the proband, at 62 years of age had a hemicolectomy for adenocarcinoma of the cecum in 1949. At the last report she was living and well at the age of 66 years.

III-18, a maternal aunt, had a benign rectal polyp removed at 46 years of age (in 1948) and a cervical polyp removed at 48 years of age (in 1950).

The conditions of III-14 and III-18 are confirmed pathologically.

The maternal side of the pedigree is unusual for its concentration of cholecystitis. The maternal relatives have been traced to the grandparents.

II-6, the maternal grandfather, was born in Poland in 1857 and also came to Minnesota. He died in 1945, aged 87 years, from a cerebral hemorrhage. He had suffered with arteriosclerosis for 25 years prior to death.

II-7, the maternal grandmother, was born in Germany in 1861 and died in Minnesota in 1937, aged 76 years, of acute cholecystitis and diabetes mellitus. She had suffered with diabetes for five years previous to death. These conditions are verified by death certificates.

II-7 had one sister, II-8, and one brother, II-9, both of whom are reported to have died of "natural" causes.

II-6 and II-7 had six children, all of whom are now living.

III-13, a maternal uncle, was 65 years old and had had no illnesses during life.

III-14, the mother of the proband, underwent a cholecystectomy one year previous to her operation for cancer of the cecum. At that time she was 61 years old and had chronic cholecystitis.

III-15, a maternal aunt, was 60 years old. At 44 years of age she had a cholecystectomy for gallbladder trouble. At 58 years of age she developed coronary heart trouble.

III-16, a maternal aunt, was 56 years old. At 48 years of age she had a cholecystectomy for cholelithiasis. At 56 years of age she developed mild diabetes mellitus. A gastrointestinal series at this time showed that she had a deformed duodenal bulb, but an ulcer was not diagnosed.

III-17, a maternal uncle, was 52 years old. He reported that at the age of 45 years he began to suffer with periodic attacks of indigestion, and at 52 years of age he was placed on a diet for a gastric ulcer.

III-18, a maternal aunt, was 50 years old. Like her sisters she also underwent a cholecystectomy for cholecystitis. This was in 1928, when she was 28 years old. In 1949 a gastrointestinal examination revealed that she had a prepyloric gastric ulcer which was cured after a year of strict diet.

The affected individuals of this sibship have reported that they have extremely nervous dispositions and are inclined to worry a great deal.

No illnesses have been reported in the maternal cousins of the proband. One, IV-61, is reported by his father to be "nervous."

On the paternal side of the family one case of cholecystitis, the paternal grandmother, II-2, and one case of gastric ulcer, the paternal uncle, III-7, have already been mentioned. One paternal cousin, IV-17, is also known to have had significant trouble. At 37 years of age he was diagnosed as having cholecystitis, but an x-ray examination showed a normally functioning gallbladder without stones. At 46 years of age a gastrointestinal examination revealed a small active duodenal ulcer. Dietary regime improved this condition temporarily, but the patient had a recurrence the next year. He now follows a strict diet for the condition. He also reports that he is strongly inclined to worry and suffer with his nerves.

The proband, IV-27, was born in 1911 and reported that she, as well as all of her sibs, had a tendency toward stomach trouble. She began to suffer with stomach upsets at 18 years of age, and when she was 24 years old she was placed on a bland diet for two months for a gastric ulcer. She followed this diet periodically until she was 31 years old, when her gastric distress increased and a physician again placed her on a bland diet for a gastric ulcer. Since that time she has controlled her condition with self-medication. Her last examination at 38 years of age revealed a negative gastrointestinal series.

The proband's brother, IV-26, was born in 1910. At 32 years of age a gastrointestinal examination revealed a duodenal ulcer which healed with medication. At 39 years of age he had another gastrointestinal series as well as a gallbladder series. The report at this time was "gastroduodenitis, with increase in the rugae and hyperplasia of the gastric mucous membrane, a spastic duodenal bulb, without definite evidence of stones in the gallbladder."

The proband's sister, IV-28, was born in 1912 and had a cholecystectomy for cholelithiasis and chronic cholecystitis at 37 years of age. She has reported no other illnesses.

Another brother, IV-29, was born in 1914 and is reported to have been treated for an "ulcer." It has not been possible to obtain further information on this relative.

No illnesses are known for the younger brothers of the proband. IV-30 was born in 1916; IV-31, in 1918; IV-32, in 1920; and IV-34, in 1926. The proband's other sister, IV-33, was born in 1922 and her only illness has been an attack of poliomyelitis at 11 years of age. However, she has reported that she tends to suffer depressive moods and is frequently bothered with her nerves.

DISCUSSION

A total of 135 individuals of blood relationship are now reported in this family history. The cousins and more distant collateral relatives of the proband have been

TABLE 1.—CASES OF CANCER REPORTED IN THE FAMILY HISTORY

Number of Affected Individual and Relationship to Proband	Age in Years		Site of Cancer	Confirmation
	Onset	Death		
II-4: Paternal great aunt		65±	Stomach	
II-5: Paternal great uncle		84	Prostate gland	Death certificate
III-1: Paternal uncle	53	54	Stomach	Death certificate
III-3: Paternal uncle	63	64	Stomach (pylorus)	Death certificate
III-5: Father	56	57	Stomach	Hospital exam (clinical); death certificate
III-6: Paternal aunt		45	Stomach	Death certificate
III-7: Paternal uncle	48	49	Stomach	Death certificate
III-9: Paternal uncle	65	66	Prostate gland	Hospital exam (clinical); death certificate
IV-21: Paternal first cousin (♀)	34	35	Large intestine	
III-14: Mother	62		Cecum	Pathology examination
III-3a: Not related (♀)	58	60	Breast	Death certificate

traced in only a few instances, so that more individuals are known to be in the family. However, relatives who have been traced are not aware of any cases of cancer in the untraced individuals.

Ten cases of cancer have been reported in the family (table 1). This represents 7.4% of the total individuals known in the history. Six of these cases are reported to be cancer of the stomach, equivalent to 4.4% of the individuals in the history. Five of the six cases of gastric cancer have been confirmed by death certificates. The other four cases of cancer involve the large intestine (two) and the prostate gland (two). Three of these four cases of cancer now have been verified by death certificates.

A pathology report has been obtained for only one case of cancer, adenocarcinoma of the cecum in the proband's mother. Only two other individuals were hospitalized. These were the proband's father, who had inoperable carcinoma of the stomach, and a paternal uncle, who had advanced carcinoma of the prostate gland. Without pathological confirmations the cases of cancer may always be questioned. However, in most cases several relatives of affected individuals have reported the cancers from information given to the family by physicians, and death certificates confirming their reports have been obtained for eight of the ten affected individuals. In the absence of other sources of information, it seems reasonable to assume that the data given for affected members of the family are reasonably accurate.

The concentration of cancer in the paternal branch of the family is striking, but the localization of cancer in the gastrointestinal tract is even more significant. This family history now exhibits one of the highest percentage frequencies for cancer of the stomach which has been reported in a family group. Histories of localization of cancer in the gastrointestinal tract have been reported by other investigators (Hauser

and Weller, 1936; Gardner and Stephens, 1950; Woolf and Gardner, 1950; and Gardner and Woolf, 1952).

The earliest case of gastric cancer in this history occurred in a female who died at 45 years of age. We have arbitrarily selected forty years of age as the "gastric cancer age" in this family group. At present 32 individuals in the history are known to be past forty years of age. The frequency of all types of cancer in these individuals is 28.1%, and the frequency of gastric cancer is 18.8%. Considering only the paternal side, in which the gastric cancer is localized, nineteen members are included in the first three generations. Eight of these individuals, 42.1%, are reported to have died with cancer, and six or 31.6% are reported to have had gastric cancer.

The paternal sibship of the third generation may be more profitably evaluated by considering their survival time, since the incidence of gastric cancer increases with age. Only one deceased individual is known to have lived past 45 years of age without developing some type of cancer before death. Two sibs are still living, aged 70 and 62 years at the last report; neither have shown any sign of cancer.

The tendency for localization of gastric cancer in this family group is much greater than was found previously in a familial study of 86 white probands with gastric carcinoma and 58 white control probands (Hagy, 1954). In the latter work the relatives of the gastric carcinoma probands showed a frequency of 1.2% affected with gastric cancer, while 0.5% of the relatives of control probands were affected with this illness. The present incidence of 4.4% gastric cancer in the family group now being reported is nearly four times as great as the frequency found in relatives of gastric carcinoma probands and over eight times as great as the 0.5% frequency found in relatives of the control probands.

In Denmark, Videbaek and Mosbech (1954) found a percentage incidence of 4.5% for gastric carcinoma among relatives of 302 probands with gastric carcinoma. In a series of 390 control probands they found an incidence of 1.2% gastric carcinoma. They conclude that the predisposition to gastric carcinoma is inherited, but that unknown exogenous factors (such as diet, gastric ulcer, occupation, etc.) may accelerate its development.

Ivy (1955) suggests that mucosal cells of the stomach which are genetically susceptible to a malignant change may be affected by nonspecific irritants or a specific gastric carcinogen. His work on rats indicates that overheated fats contain a low-grade carcinogen when given subcutaneously, and certain certified food dyes and hot drinks and foods should be suspected as dietary factors important as gastric irritants. Much more investigation is needed on this aspect of the problem.

The part of the family group in which cancer is localized is diagrammed separately in figure 2. As far as is known the environments of these individuals were relatively constant. For the most part they and their ancestors have followed farming occupations. The probability for genetic factors being important in causation of the neoplasia seems likely although unknown environmental influences must still be considered. A tendency for a gastric weakness among these individuals appears definite since five sibs developed cancer of the stomach. The spouses of the affected sibs are not reported in any case, except the proband's mother, to have developed any type of cancer. This further accentuates the likelihood of genetic factors as the basic cause

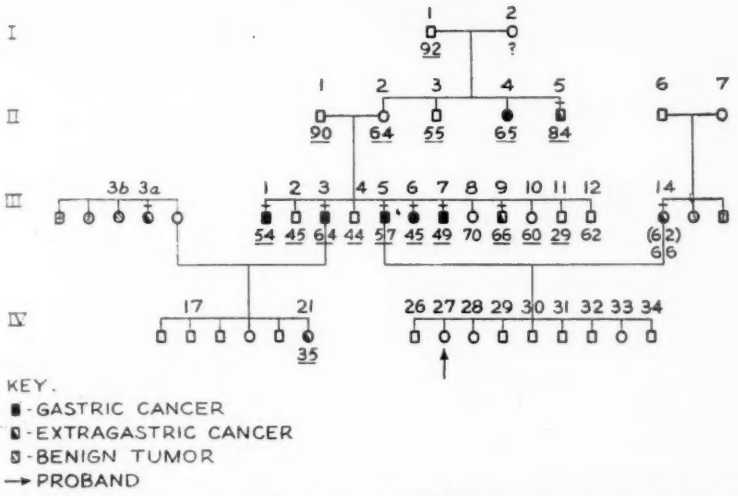

FIG. 2. Cases of cancer in the family history. Numbers above symbols correspond to the individual's number on fig. 1. Numbers below symbols represent age at death when underlined or the living age when not underlined. Numbers within symbols represent the number of unaffected individuals. An additional line above a symbol represents a confirmed case of cancer.

of the neoplasia among the related members of this family group. The type of inheritance which may be involved in this history is not readily determined from the few generations that have reached the gastric cancer age. In figure 2, the type of inheritance of a tendency for gastric cancer could be recessive or it can be explained as a dominant with decreased penetrance. The family group must be followed in the future to determine a specific genic or environmental expression.

One individual in the fourth generation died of cancer of the lower intestine at 35 years of age, which is an earlier onset than in the preceding generations. Cases of neoplasia have been reported in both the paternal and maternal branches of this individual's family.

The tendency for cholecystitis is equally striking in this family group, particularly on the maternal side of the proband's family. In figure 3, the part of the family group affected with cholecystitis has been diagrammed. Some type of gallbladder trouble has been reported for seven members of the family (table 2). This is a frequency of 5.2%. Two additional individuals have had symptoms of cholecystitis. Only one individual, the proband's mother, has had both cancer (of the cecum) and cholecystitis.

On the maternal side the proband's grandmother and all four of the proband's aunts suffered with cholecystitis. In one aunt and a sister of the proband cholecystitis was associated with cholelithiasis. On the paternal side the proband's mother died of cholelithiasis. A male paternal first cousin formerly had symptoms of gallbladder trouble and the proband's brother may have gallbladder dysfunction.

In this history a majority of females are affected with cholecystitis. Other investi-

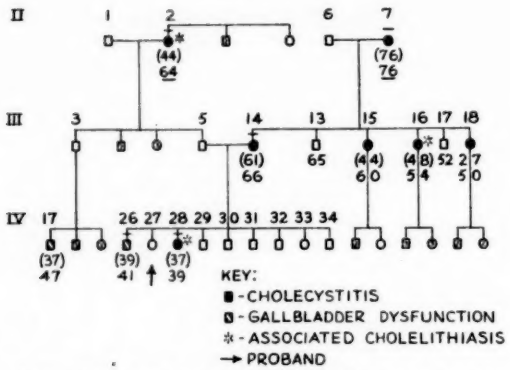

FIG. 3. Cases of cholecystitis in the family history. Numbers above symbols correspond to the individual's number on fig. 1. Numbers in parenthesis below symbols represent onset age. Numbers not in parenthesis below symbols represent present age, or age at death if underlined. Numbers within symbols represent number of unaffected individuals. An additional line above a symbol represents a confirmed case of cholecystitis.

TABLE 2.—CASES OF CHOLECYSTITIS REPORTED IN THE FAMILY HISTORY

Number of Affected Individual and Relationship to Proband	Age in Years		Associated with Cholelithiasis	Confirmation
	Treated	Current		
II-7: Maternal grandmother	76	d. 76	?	Death certificate
III-14: Mother	61	66	no	Pathology report
III-15: Maternal aunt	44	60	?	
III-16: Maternal aunt	48	54	yes	
III-18: Maternal aunt	27	50	?	
II-2: Paternal grandmother	44±	d. 64	?	Death certificate
IV-28: Sister	37	39	yes	Pathology report
IV-26: Brother (?)	39	41	no	Gallbladder series
IV-17: Paternal first cousin (♂) (?)	37	47	no	Gallbladder series

Questionable cases are discussed in the text.

gators have mentioned that women are more frequently affected with cholecystitis than are men (Draper, 1935; Bell, 1940). It is not possible to determine definitely a specific mode of inheritance in the present history, but the concentration of cases indicates that heredity may be of significance. A neurogenic factor also should be considered, since the living affected members have all reported nervous dispositions.

Several family histories of cholecystitis are recorded. Marcuse (1929) reported a Jewish family in which seventeen members in five generations were affected with cholecystitis or cholelithiasis. Huddy (1925) reported another family in which these conditions occurred in six members in three generations.

Cases of ulcer have been more sporadic among members of the family than cases of cancer or cholecystitis. Members in both the maternal and paternal branches have been affected with peptic ulcer (figure 4, table 3).

Four cases of gastric ulcer are now reported, including the proband, her paternal

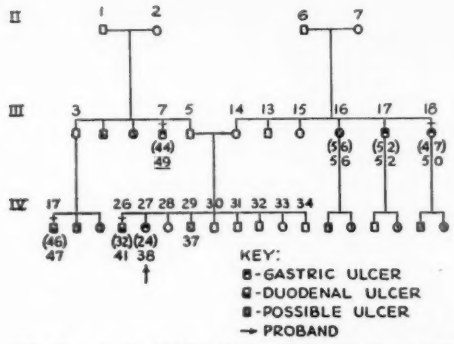

FIG. 4. Cases of peptic ulcer in the family history. Numbers above symbols correspond to the individual's number on fig. 1. Numbers in parenthesis below symbols represent onset age. Numbers not in parenthesis below symbols represent present age, or age at death if underlined. Numbers within symbols represent number of unaffected individuals. An additional line above a symbol represents a confirmed case of ulcer.

TABLE 3.—CASES OF PEPTIC ULCER REPORTED IN THE FAMILY HISTORY

Number of Affected Individual and Relationship to Proband	Age in Years		Site of Ulcer	Confirmation
	Treated	Current		
III-7: Paternal uncle	44	d. 49	Stomach	Death certificate
IV-17: Paternal first cousin (♂)	46	47	Duodenum	Gastrointestinal series
III-17: Maternal uncle	52	52	Stomach	
III-18: Maternal aunt	47	50	Stomach	Gastrointestinal series
III-16: Maternal aunt (?)	56	56	Duodenum	Gastrointestinal series, "deformed duodenal bulb"
IV-26: Brother	32	41	Duodenum	Gastrointestinal series
IV-27: Proband	24	38	Stomach	
IV-29: Brother (?)	?	37	Stomach or duodenum	

Questionable cases are discussed in the text.

uncle who died of gastric cancer five years later, and her maternal uncle and maternal aunt. Two cases of duodenal ulcer are now included in the history. Those affected are the proband's brother and a male paternal first cousin. A maternal aunt was found to have a "deformed duodenal bulb without a definite ulcer crater" through a gastrointestinal examination. The proband reported that another brother had an ulcer, but the site, stomach or duodenum, was not known to her.

Helweg-Larsen (1946) reported a family group in which twenty-seven members had some type of gastroduodenitis. Seven individuals were known to have gastric ulcer and five had duodenal ulcer. Among these individuals there appeared to be a simple dominant hereditary disposition that gave rise to gastroduodenitis associated either with or without peptic ulcer. The familial study of Doll and Kellock (1951) indicates that genetic factors are related in the development of peptic ulcer and that the mode of inheritance of a tendency for gastric and duodenal ulcers may be differ-

ent. Carter (1953) reports that the sex incidence in duodenal ulcer is about four males to one female affected, while in gastric ulcer approximately a one to one sex ratio is now being found. It is difficult to separate environmental and genetic factors in peptic ulcers and the basic interaction of exogenous and endogenous factors in the causation of a duodenal or gastric ulcer could be very complex. The specific relationship of peptic ulcer to gastric carcinoma is not known (Ewing, 1940). Ivy (1955) believes that a gastric carcinoma may arise from a gastric ulcer. Menasci (1930) described a history of peptic ulcers associated with gastric cancer. Follow-up studies of patients with gastric ulcer have not shown a particularly high incidence of gastric carcinoma (Hsiao-Ch'ien, 1936; Walton, 1936; Martin and Lewis, 1949).

Two cases of diabetes mellitus are reported in individuals who have lived either to or past the fifth decade (II-7 and III-16), so that related members of these individuals should also be followed for this disease.

At present the sibship which includes the proband is of greatest importance, since its members seem particularly disposed genetically toward the development of conditions which appear to be concentrated in this family group. The members of this sibship receive a tendency for gastric cancer from the paternal side and a tenddency for cholecystitis from the maternal side of the family. Cases of duodenal and gastric ulcers have been reported in both paternal and maternal relatives. The mother of these sibs has had both cancer and cholecystitis. These sibs are now in their third and fourth decades. The three oldest members have been treated for either a peptic ulcer or cholecystitis. Any symptoms of these conditions which the younger members may manifest should be fully evaluated. These individuals need also to be made cognizant of danger signals of cancer, particularly cancer of the gastrointestinal tract. Complete physical examinations at frequent intervals may help to avoid some of the illnesses from which their ancestors have suffered and to which these individuals appear more susceptible than the general population.

We hope to follow the living relatives more closely in the future. A more detailed study of both the paternal and maternal cousins of the proband still needs to be made. For a complete genetic evaluation, the living members of this family group need to be followed in the years to come. Our present knowledge may lead to early diagnosis of some of the conditions which they may develop. While we cannot say with certainty that any additional individual in this history will develop a cancer, an ulcer, or cholecystitis, if genetic factors are important in determining the expression of these illnesses, the susceptibility of various members of the family group appears greatly increased.

SUMMARY

A family group has been investigated in which ten members (nine on the paternal side) are affected with cancer, representing 7.4% of the individuals now known in the history. Six of these have had gastric cancer (4.4%). This frequency of gastric cancer is nearly four times as great as the incidence of gastric cancer observed among relatives of eighty-six gastric carcinoma probands and over eight times as great as the incidence observed among relatives of fifty-eight non-cancer probands. Forty years of age has been taken as the "gastric cancer age" in this family group. The

frequency of all types of cancer in individuals past this age is 28.1% and the frequency of gastric cancer is 18.8%. Eight of nineteen paternal members of the first three generations died of cancer (42%) and six of these (31.6%) had gastric cancer. Four cases of gastric ulcer and two cases of duodenal ulcer have been reported among the relatives; one individual developed a gastric ulcer five years prior to death from gastric carcinoma. The tendency for cholecystitis is equally striking in the history with seven individuals affected (5.2%). Five of these are on the maternal side of the family. Two maternal relatives have developed diabetes mellitus. The proband and her eight sibs are in their third and fourth decades. The proband suffers with a gastric ulcer, a brother with a duodenal ulcer, a sister has had a cholecystectomy, and another brother is reported to have an ulcer.

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Possible Genetic Carriers in the Spherophakia-Brachymorphia Syndrome*

H. WARNER KLOEPFER, AND J. WILLIAM ROSENTHAL

INTRODUCTION

The spherophakia-brachymorphia syndrome was first recognized by Marchesani (1939) to be distinct from Marfan's syndrome. This syndrome is characterized by spherophakia, brachydactyly, microphakia, ectopia lentis, glaucoma and myopia; the present investigation has identified a large *atd* angle of the palmar dermatoglyphics (fig. 4) as an additional stigma.

Marchesani believed the severe form of the syndrome to depend upon homozygous genes and the less severe form to be single gene effects. In subsequent studies by other authors a dominant mode of inheritance was suggested in two families and the recessive mode of inheritance first postulated was supported in 8 families. Although short fingers and short stature have been observed frequently in parents and siblings of affected individuals few anthropometric data on non-affected relatives have been reported. Neel (1947) directed attention to the importance of detecting genetic carriers of inherited diseases. In no study of the recessive type of spherophakia-brachymorphia syndrome has an attempt been made to define precisely the possible characteristics of the heterozygous carrier as distinct from the homozygous normal and homozygous affected.

The purposes of the present study are: (1) to report certain anthropometric and ophthalmic observations made in 5 fully affected individuals and their relatives; (2) to suggest stigmata which may be useful in distinguishing heterozygous carriers from homozygous normals and homozygous affected. Pedigrees showing the relationships of all individuals in this study are given in figures 1 and 2. Original data are listed in tables 13 and 14.

HISTORY

The following review of literature is limited to the criteria found useful in selecting heterozygotes. "Normal" describes individuals who in the light of the present study may have been normal homozygotes or heterozygous carriers.

Among 8 cases of supposed Marfan's syndrome Weill (1932) recorded the case of a 42-year-old affected female who was 142 cm. tall and had "short swollen fingers with extremities permitting only imperfect opening and closing."

Marchesani (1939) reported a study of 2 families. In 1 family the syndrome occurred in an 8-year-old male with stature of 108 cm., shortened fingers and toes, and thick musculature. The normal father was 158 cm. tall and had short plump hands and fingers. The normal mother was 153 cm. tall and had small hands. Three

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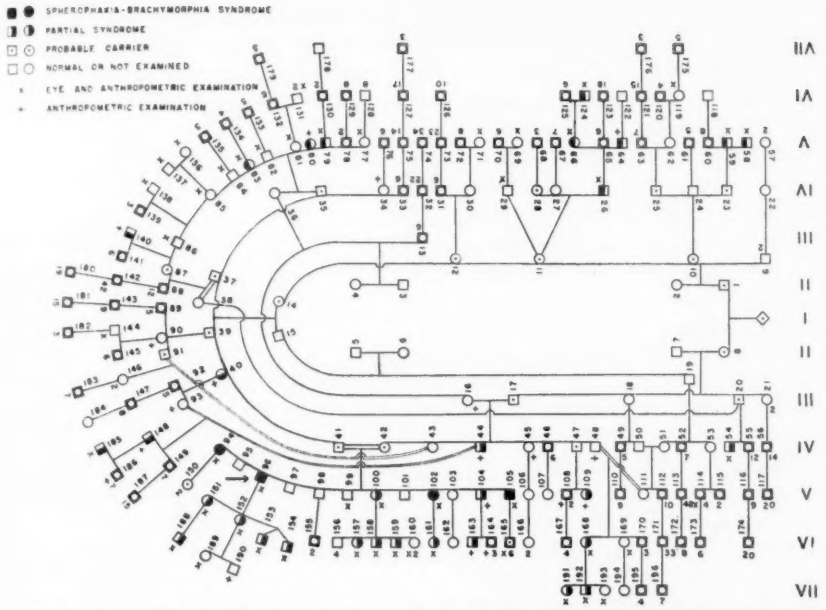

FIG. 1. Pedigree of Kindred 1 showing recessive type of spherophakia-brachymorphia in a family of French descent with partial syndrome caused by single gene. Reference numbers of individuals are above the symbols; numbers below the symbols are the numbers of individuals, if more than one, represented by a single symbol.

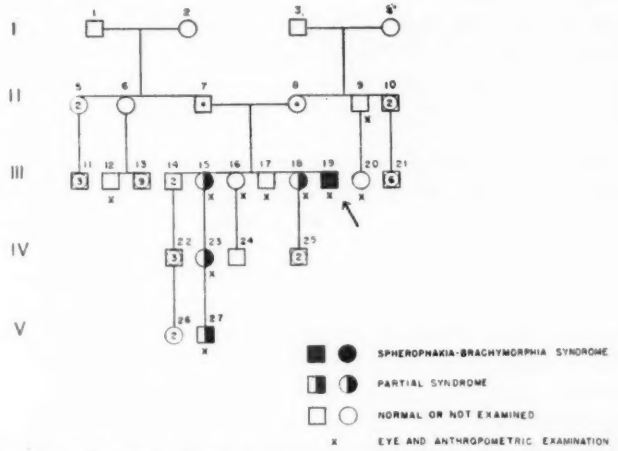

FIG. 2. Pedigree of Kindred 2 showing recessive type of spherophakia-brachymorphia in a family of Italian descent with partial syndrome caused by a single gene. Reference numbers of individuals are above the symbols; numbers within symbols are the numbers of individuals, if more than one, represented by a single symbol.

of the father's 6 living siblings were small and 3 were normal or large. Four siblings of the mother were normal. In Marchesani's second family a 36-year-old affected male whose stature was 147 cm. had relatively short hands and fingers. A 38-year-old affected brother was 156 cm. tall and had small hands. A 33-year-old affected sister with small hands was 153 cm. tall. A normal 38-year-old sister was 150 cm. tall and a normal 32-year-old brother was 152 cm. tall but had small hands. The deceased father was reported to be normal and 160 cm. tall. The 69-year-old normal mother was 150 cm. tall.

Meyer and Holstein (1941) observed 4 cases of spherophakia-brachymorphia and 2 normal siblings in a family whose parents were first cousins. A 17-year-old affected female was 138.4 cm. tall and had stubby hands, short fingers, short tibia, short feet and short toes. A 26-year-old affected sister was 141.0 cm. tall. A 23-year-old affected sister was 138.4 cm. tall and a 21-year-old affected brother was 144.8 cm. tall. The 2 normal brothers were of normal height. The statures of the father and mother were 163.8 and 148.6 cm., respectively. These authors accepted the mode of inhertance proposed by Marchesani.

Schmid (1946) recorded the occurrence of spherophakia-brachymorphia in a 17-year-old male who had a stature of 158 cm., diminished span, and had short hands and feet; his father and mother were 164 and 151 cm. tall.

Diethelm (1947) observed 2 cases in a family of 3 children whose parents were first cousins. Complete anthropometric observations were included in his study. A 30-year-old affected female had a stature of 161 cm., span 161.5 cm., hand length 17 cm., and hand width 7.5 cm. Digits I to V measured 60, 66, 74, 76 and 56 mm. The 25-year-old affected brother had a stature of 163 cm., small hands and "exaggerated" span. The normal 28-year-old sister had a stature of 165 cm., span of 173 cm., and bilateral myopia of -3.00. The 56-year-old father had a stature of 170 cm., span 179 cm., medium-sized hands with strong fingers. Legs were well formed. The 59-year-old mother had a stature of 162 cm., span 165, and wide but well formed hands. Right and left lenses of glasses were -6.75 and -11.00 sphere. A 59-year-old paternal uncle of affected had a stature of 169 cm. and presbyopia. A 57-year-old uncle had a stature of 172 cm., strong hands and legs, and bilateral myopia of -2.00. A recessive mode of inheritance for the full syndrome was considered certain.

Stadlin and Klein (1948) recorded the occurrence of spherophakia-brachymorphia in an 18-year-old girl whose parents were first cousins. The affected girl had a stature of 160 cm., span 160, hand length 17.5 cm., strong legs and feet, and a peculiar walk. A normal sister was 146 cm. tall and of brachymorphic type. The normal father had very short hands and feet. The mother was short and stocky. In accord with previous authors, Stadlin and Klein accepted the mode of inheritance proposed by Marchesani and they believed small height or "brachymorphia" was a characteristic of heterozygotes.

Rousseau (1949) reported 9 cases of spherophakia-brachymorphia covering 4 generations. The eye and anthropometric findings in this family did not appear to differ from those in families of the recessive type.

Seeleman (1949) observed a 3-year-old boy with stature of 79 cm., plump extremities, abnormal shortness of fingers and toes which could be flexed only slightly. The mother was 160 cm. tall.

Arjona (1952) reported 2 cases of spherophakia-brachymorphia in one family and one case in another. In one family the cousin parents had a 24-year-old affected daughter and a 29-year-old affected son who were both short and brachydactylous. No details were recorded about the 6 normal siblings and the parents. In another family, in which the parents were second cousins, Arjona observed a 16-year-old female with the syndrome. No anthropometric observations were reported in the patient, 4 normal brothers, or normal parents.

Probert (1953) found spherophakia-brachymorphia in a family but was uncertain about the mode of inheritance. A 42-year-old affected female had minimi that were shorter than normal. A 38-year-old brother had normal eyes but very short stature and short extremities. A 37-year-old affected sister had short fifth digits like her affected sister. A 26-year-old affected sister had brachyphalangy. A 24-year-old affected brother had shortened little fingers. The mother, a maternal uncle, a maternal aunt, and the maternal grandmother had brachyphalangy or brachydactyly. Four of the 7 children of the brachydactylous maternal uncle also had brachydactyly. No anthropometric observations were recorded for any members of the family and eye findings were limited to 5 of the 6 siblings.

Rosenthal and Kloepfer (1955) gave a full clinical report on eye findings and therapy of the 5 cases of spherophakia-brachymorphia included in the present study.

CRITERIA USED IN SELECTING HETEROZYGOTES

The criteria used to select heterozygotes were: (1) a related individual who possessed two or more stigmata of the syndrome, (2) the offspring or parent (assumed heterozygous) of a fully affected homozygote, or (3) the parent of a heterozygous child related to the propositus and possessing one or more stigmata of the syndrome. The 4 stigmata used in this study are believed to be the effects of a single gene; eye departures from normal in the direction of the syndrome, short stature, short fingers, and large *atd* angle.

Eye departures from normal in the direction of the syndrome were compound myopic astigmatism, myopic astigmatism, or simple myopia of more than 1 diopter. These deviations from normal were listed by Thorington (1944) to be expected in 8 percent, 1.5 percent and 1.5 percent, respectively, of the general population. A fraction of $\frac{1}{9}$ was used to calculate the expectation of encountering one of these slight departures in a person chosen at random.

Stature short enough to be expected approximately in $\frac{1}{20}$ or less in a random population was considered to be a second stigma of the syndrome. The means and standard deviations of stature based on American studies as listed by Watson and Lowrey (1951) were used as norms. Statistical tables which give the expectation of obtaining various deviations in a given direction from the mean were used to calculate the chance that the height of a relative would be a given distance below the norm. These calculations were later combined with those for other criteria to obtain the total chance occurrence of a particular partial syndrome on the assumption that the various stigmata are independent of one another.

Finger-palm index small enough to be expected approximately in $\frac{1}{7}$ or less of the control population was considered to be a third stigma of the syndrome. At the beginning of the investigation norms for means and standard deviations of finger-palm

index obtained from outline drawings were not available and an index of 73 or less was arbitrarily chosen in both sexes to indicate a deviation in the direction of the syndrome. After the heterozygous individuals were separated from the normal homozygous group, the finger-plam index values of the normal homozygotes were combined with index values of a non-related group to give a larger control group from which means and standard deviations were calculated separately for each sex. Using these values as norms, finger-palm index values small enough to be expected in 1/7 or less of the control population were considered to be deviations in the direction of the syndrome.

A sum of *atd* angles of the right and left hands large enough to be expected approximately 1/9 or less in a random population was considered to be a deviation in the direction of the syndrome and a fourth stigma. The means and standard deviations of *atd* angles as listed by Penrose (1954) were used as norms and his directions were followed to determine the size of the *atd* angles.

In a manner similar to that described for short stature the chance of obtaining finger-palm index values as small or smaller and the chance of obtaining *atd* angles as large or larger were determined for each person. When values for all 4 criteria were available the product of the 4 separate probabilities of obtaining each combination of stigmata, including a value of 1 or 1/9 for eye stigmata and counting a value of 1 for each stigma known to be absent, ranged from 4.2×10^{-3} to 5.8×10^{-10} in the group believed to be heterozygous; corresponding values ranged from 1 to 4.0×10^{-3} in the group believed to be homozygous normal. Probabilities of encountering an individual in the general population with stigmata deviating as much as or more in the direction of the syndrome were recorded in tables 10 and 11.

EYE

Eye examinations included determination of visual acuity, intraocular pressure and extraocular muscle function as well as external and ophthalmoscopic examination. Myopic refractive errors of more than 1.00 diopter were considered departures in the direction of the syndrome. The number of heterozygous carriers and homozygous normal individuals who were found to be myopic, hyperopic, and with miscellaneous insignificant ocular findings is given in table 1.

TABLE 1.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND EYE DEPARTURES IN THE DIRECTION OF THE SYNDROME

Numbers in column under "Misc." represents individuals with miscellaneous insignificant ocular findings. Column under "Ratio" indicates the ratio between the observed number of individuals with eye departures in the direction of the syndrome and the number expected in a random population. *Carrier* refers to heterozygotes who have one normal gene and one gene for spherophakia-brachymorphia. *Normal* represents normal homozygotes who are not known to carry any genes for the syndrome.

Group	Sex	Myopia	Hyperopia	Misc.	Total	Ratio
Carrier	♂	5	1	10	16	2.8
Carrier	♀	7	1	6	14	4.5
Normal	♂	1	2	13	16	.6
Normal	♀	2	1	10	13	1.4

Among 16 heterozygous males, 5 had eye departures in the direction of the syndrome (1-79, 1-124, 1-154, 1-165b, and 1-188), 1 had hyperopia (1-58), and 10 had miscellaneous ocular findings (1-26, 1-54, 1-59, 1-153, 1-158, 1-159, 1-165d, 1-185, 1-192, and 2-27). (Note: Reference numbers to individuals correspond to those used in all figures and tables. The first digit of a reference number, set off by a hyphen, refers to pedigree 1 or 2.) Among 14 heterozygous females, 7 had eye departures in the direction of the syndrome (1-83, 1-100, 1-151, 1-152, 1-157, 1-161, and 2-23), 1 had hyperopia (1-191), and 6 had miscellaneous ocular findings (1-66, 1-165a, 1-165c, 1-168, 2-15, and 2-18). Eye departures in the direction of the syndrome occurred 3.6× the frequency expected in the general population ($12 \div {}^{3}\%_{9}$) when the two sexes were combined.

Among 16 homozygous normal males, 1 (1-99) had eye departures in the direction of the syndrome, 2 had hyperopia (1-82 and 1-84), and 13 had miscellaneous ocular findings (1-29, 1-86, 1-114b, 1-114c, 1-114d, 1-131a, 1-131b, 1-137, 1-138, 1-144, 2-9, 2-12, and 2-17). Among 13 homozygous normal females, 2 had eye departures in the direction of the syndrome (1-69, and 1-136), 1 had hyperopia (1-81), and 10 had miscellaneous ocular findings (1-71, 1-77, 1-85, 1-114a, 1-119, 1-160a, 1-169, 1-193, 2-16, and 2-20). Spherophakia was probably present in (1-136). Eye departures in the direction of the syndrome occurred in almost exactly the same proportion as expected in the general population ($3 \div {}^{2}\%_{9} = .9$) when the two sexes were combined.

The probability of finding as many as 12 individuals out of a sample of 30 with eye departures in the direction of the syndrome would be expected less than once in 17,000 in a randomly selected population. Consequently, an eye departure in the direction of the syndrome is believed to be one of the stigmata of heterozygous carriers.

STATURE

According to Watson and Lowrey (1951) 17-year-old American males have a mean stature of 176.6 ± 5.8 cm. and 17-year-old females have a mean stature of 165.5 ± 5.1 cm. Using these figures as norms a ***short*** adult is defined in this study as having a stature between one and two standard deviations below the mean which for males is 165.1 to 170.8 cm. and for females is 155.4 to 160.4 cm. A very short adult has a stature of two or more standard deviations below the mean which for males is 165.0 cm. and for females is ≤155.3 cm. Means and standard deviations for lower age levels may be used to classify individuals under 17 into groups of short, very short and average stature. In a random population of Americans one would expect approximately $\frac{1}{7}$ to be short and $\frac{1}{44}$ to be very short. The range, mean and standard deviation of stature values for the various groups are given in table 2.

The statures of the 3 cases of spherophakia-brachymorphia reported in this study and the statures of 5 previously reported adult males ranged from 145 to 163 cm. with a mean and standard deviation of 153.5 ± 5.5 cm. The stature of 9 fully affected adult females, based on 2 cases reported in this study and 7 previously reported, ranged from 138 to 161 cm. with a mean of 145.6 ± 9.2. Thus all cases with the full syndrome were very short with the exception of 2 females who were one standard

TABLE 2.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND STATURE

Syndrome refers to affected homozygotes who have two genes for the syndrome. *Carrier* refers to heterozygotes who have one normal gene and one gene for spherophakia-brachymorphia. *Normal* represents normal homozygotes who are not known to carry any genes for the syndrome. Values for the "control" group were obtained from Watson and Lowrey (1951).

Group	New Cases	Previously Reported	Total	Sex	Range (cm)	Mean and Standard Deviation
Syndrome	3	5	8	♂	145–163	153.5 ± 5.5
Syndrome	2	7	9	♀	138–161	145.6 ± 9.2
Carrier	7	5	12	♂	153–170	162.6 ± 4.8
Carrier	10	6	16	♀	133–162	151.8 ± 7.1
Normal	8		8	♂	159–176	169.2 ± 6.2
Normal	7		7	♀	157–166	159.4 ± 4.4
Control			100	♂		176.6 ± 5.8
Control			100	♀		165.5 ± 5.1

deviation below the mean, instead of two or more. People with very short stature occurred 38.8 × the frequency expected in the general population (15 ÷ $^{17}/_{44}$).

The statures of 7 heterozygous adult males (1-44, 1-104, and with age adjustments 1-153, 1-154, 1-163, 1-165b, and 1-192) plus the statures of 5 previously reported fathers of fully affected offspring, ranged from 153 to 170 cm. (4 short, 8 very short) with a mean of 162.6 ± 4.8. The statures of 10 heterozygous adult females (1-80, 1-100, 1-151, 1-152, 1-161, 1-168, 2-15, 2-18, 2-23, and with age adjustment 1-191) plus statures of 6 previously reported mothers of fully affected offspring, ranged from 133 to 162 (4 short, 11 very short, 1 average) with a mean of 151.8 ± 7.1. Very short stature occurred 29.9 × the frequency expected by chance (19 ÷ $^{28}/_{44}$).

The statures of 8 normal homozygous adult males (1-99, 1-114b, 1-114c, 1-114d, 1-164b, 2-9, 2-12 and 2-17) ranged from 159 to 176.0 (2 short, 2 very short, 4 average) with a mean of 169.2 ± 6.2. The statures of 7 normal homozygous adult females (1-71, 1-114a, 1-164a, 1-169, 2-16, 2-20, and with age adjustment 164c) ranged from 157 to 166 (3 short, 1 very short, 3 average) with a mean of 159.4 ± 4.4.

The means and variances of various groups were compared with one another to determine whether differences between them were statistically significant (table 3).

With the exception of comparison 1, the stature of males was significantly higher than that of females in all comparisons and the size of the standard deviations in the sexes was similar (comparisons 1, 4, 7 and 12). It would seem that the sexes should be considered separately in all comparisons. The presence of 2 genes for spherophakia-brachymorphia in contrast to one gene would appear to shorten stature in males but not in females (comparisons 2 and 3). A single gene seemed to lower the stature of both males and females (comparisons 5, 6, 8 and 9). The stature of normal males and females was lower than the stature of the control groups (comparisons 10 and 11). The standard deviation of carrier females was larger than the standard deviation of control females, possibly because several individuals were so very short.

The fact the normal homozygotes in these families were shorter than the controls could be due to: (1) bias of investigators in selection of members for measurements, (2) other genes or environmental factors causing an undue amount of shortness in

TABLE 3.—VALUES OF t AND F OBTAINED FROM TESTS OF SIGNIFICANCE APPLIED TO DIFFERENCES IN STATURE AND SIZE OF STANDARD DEVIATIONS AMONG THE VARIOUS GROUPS AS DESCRIBED IN TABLE 2

Number	Groups Compared	Degrees Freedom ($n_1 + n_2 - 2$)	t-value	F-value
1	Syndrome ♂♂ and syndrome ♀♀	15	2.0	2.8
2	Syndrome ♂♂ and carrier ♂♂	18	3.7**	1.4
3	Syndrome ♀♀ and carrier ♀♀	23	1.8	1.8
4	Carrier ♂♂ and carrier ♀♀	26	4.4**	2.1
5	Carrier ♂♂ and normal ♂♂	18	2.5*	1.7
6	Carrier ♀♀ and normal ♀♀	21	2.5*	2.4
7	Normal ♂♂ and normal ♀♀	13	3.2**	1.9
8	Carrier ♂♂ and control ♂♂	110	8.0**	1.4
9	Carrier ♀♀ and control ♀♀	114	9.3**	2.0*
10	Normal ♂♂ and control ♂♂	106	3.4**	1.3
11	Normal ♀♀ and control ♀♀	105	3.1**	1.2
12	Control ♂♂ and control ♀♀	198	14.3**	1.3

* .05 level of significance.
** .01 level of significance.

these families, (3) failure to detect carriers who were falsely classified in the normal group, or (4) use of a control group which was not adequate. In World War I men from the part of the United States in which these kindreds live had a stature of 172.6 ± 6.8 according to Davenport and Love (1921).

FINGER-PALM INDEX

The average finger length of a person was determined by measuring the length of each finger on each hand from outline drawings and dividing by 10. See figure 3 for an illustration of distal and proximal points on the fingers for determining finger length. Proximal limits for fingers I, II and V were determined by the intersection of perpendicular lines drawn from most proximal interdigital boundaries and lines extended from most distal finger tips through axes of fingers. Proximal limits for fingers III and IV were determined by intersection of lines connecting most proximal interdigital boundaries and lines extended from most distal finger tips through axes of fingers.

The finger-palm index was obtained by dividing the average finger length of both hands by the average palm width of both hands and multiplying by 100. Palm width was also measured from the hand outlines (see line m–n in figure 3). The range, mean and standard deviation of finger-palm indexes obtained in this study are given in table 4. The means and variances of various groups were compared with one another to determine whether differences between them were statistically significant. See table 5 for the results of these comparisons.

The mean finger-palm index for 55 males and females (31 normal homozygotes and 24 unrelated controls) was 77.8 ± 4.8. Using these figures as norms short fingers are defined as a finger-palm index value between one and two standard deviations

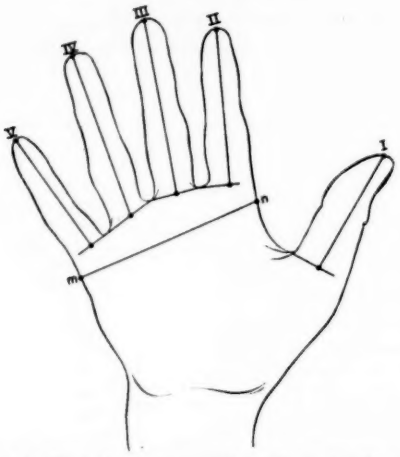

FIG. 3. Outline of hand to illustrate measurements of finger length and palm width. Proximal limits for fingers were determined by the indicated lines, and finger lengths were measured from these lines to ends of the digits. The line m-n shows the level at which palm width was measured.

TABLE 4.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND FINGER-PALM INDEX

Finger-palm index is: (average finger length × 100) ÷ average hand width. Except for three individuals the control group was selected from a population in which one or more relatives carried a gene for sickle-cell anemia.

Group	Number	Sex	Range	Mean and Standard Deviation
Syndrome	3	♂	57–69	63.5 ± 5.0
Syndrome	2	♀	55–58	56.5 ± 1.9
Syndrome	5	♂ and ♀	55–69	60.7 ± 5.3
Carrier	14	♂	62–81	71.1 ± 4.3
Carrier	15	♀	68–80	74.9 ± 3.8
Carrier	29	♂ and ♀	62–81	73.1 ± 4.5
Normal	15	♂	70–86	75.6 ± 3.9
Normal	16	♀	72–86	78.0 ± 3.6
Normal	31	♂ and ♀	70–86	76.8 ± 3.9
Control	12	♂	68–94	78.2 ± 6.4
Control	12	♀	74–85	80.3 ± 4.0
Control	24	♂ and ♀	68–94	79.2 ± 5.5

below the mean, which is 68.27 to 73.05 in this study. Very short fingers are two or more standard deviations below the mean, which is ≤ 68.26.

The finger-palm indexes of the 5 cases of spherophakia-brachymorphia syndrome reported in this study ranged from 55 to 69 with a mean of 60.7 ± 5.3.

Among 14 heterozygous males, 4 had very short fingers 1-154, 1-165b, 1-165d, and 1-192; 8 had short fingers (1-44, 1-58, 1-124, 1-153, 1-158, 1-159, 1-163, and 1-185); 2 had average length fingers (1-79, and 1-104). Finger-palm index values ranged from 62 to 81 with a mean of 71.1 ± 4.3. Among 15 heterozygous females, 1 had very

TABLE 5.—VALVES OF t AND F OBTAINED FROM TESTS OF SIGNIFICANCE APPLIED TO DIFFERENCES IN FINGER-PALM INDEXES AND SIZE OF STANDARD DEVIATIONS AMONG THE VARIOUS GROUPS

Number	Groups Compared	Degrees Freedom ($n_1 - n_2 - 2$)	t-value	F-value
1	Syndrome ♂♂ and syndrome ♀♀	3	1.5	5.4
2	Syndrome ♂♂ and carrier ♂♂	15	2.5*	1.9
3	Syndrome ♀♀ and carrier ♀♀	15	6.4**	2.2
4	All syndromes and all carriers	32	5.4**	1.7
5	Carrier ♂♂ and carrier ♀♀	27	2.5*	1.3
6	Carrier ♂♂ and normal ♂♂	27	2.9**	1.2
7	Carrier ♀♀ and normal ♀♀	29	2.3*	1.1
8	All carriers and all normals	58	3.4**	1.3
9	Normal ♂♂ and normal ♀♀	29	1.7	1.2
10	Carrier ♂♂ and control ♂♂	24	3.2**	2.3
11	Carrier ♀♀ and control ♀♀	25	3.4**	1.2
12	All carriers and all controls	51	5.1**	1.5
13	Normal ♂♂ and control ♂♂	25	1.3	2.8*
14	Normal ♀♀ and control ♀♀	26	1.5	1.3
15	All normals and all controls	53	1.9	1.9
16	Control ♂♂ and control ♀♀	22	.9	2.5

* .05 level of significance.
** .01 level of significance.

short fingers (1-168); 6 had short fingers (1-40, 1-66, 1-109, 1-152, 1-191, and 2-15); 8 had average or long fingers (1-80, 1-83, 1-100, 1-151, 1-157, 1-161, 2-18, and 2-23). Finger-palm index values ranged from 60 to 80 with a mean of 74.9 ± 3.8.

Among 15 homozygous normal males, 3 had short fingers (1-84, 1-86, and 1-114b); 12 had average or long fingers (1-82, 1-99, 1-114c, 1-114d, 1-131a, 1-131b, 1-137, 1-164b, 1-186a, 2-9, 2-12 and 2-17). Finger-palm index values ranged from 70 to 86 with a mean of 75.6 ± 3.9. Among 16 homozygous normal females, 1 had short fingers (1-193); 15 had average or long fingers (1-34, 1-45, 1-69, 1-71, 1-77, 1-81, 1-85, 1-93, 1-114a, 1-136, 1-160a, 1-164a, 1-164c, 1-169, and 2-16). Finger-palm index values ranged from 72 to 86 with a mean of 78.0 ± 3.6.

Although the finger-palm index values for males and females in comparison 1 did not differ significantly, the number of individuals in these groups was inadequate. Likewise, when these two groups were used for comparisons 2, 3 and 4 they were too small to assure valid results, but if similar values were to be obtained with larger numbers one might conclude that the presence of two genes in contrast to one gene shortened the fingers in both males and females. In like manner a single gene seems to shorten the fingers in both sexes in contrast to no gene for the syndrome (comparisons 6, 7, 8, 10, 11, and 12). When spherophakia-brachymorphia genes were absent non-significant t and F values were obtained in the sexual comparisons (9 and 16), but when a single gene was present the mean finger-palm index seemed to be lowered more in males than in females (comparison 5). Since the normal are all relatives from two families possibly they are more homogeneous than the controls taken from many families and this difference is reflected in the high F-value obtained in comparisons 13.

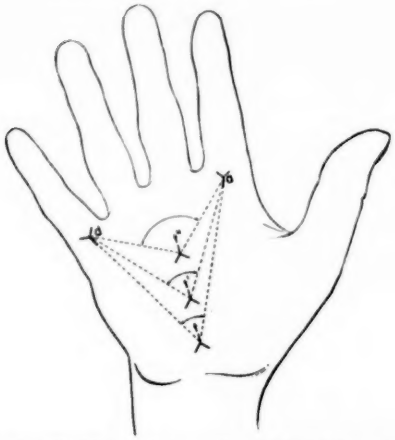

FIG. 4. The *atd* angle is described by the intersection of dotted lines extended from the a and d digital triradii to the highest axial triradius on the palm which may be located in the t, t′, or t″ position. A triradius is formed by epidermal ridges running in three directions past a common point.

atd ANGLE AND POSITION OF AXIAL TRIRADIUS

Epidermal ridges running in 3 directions past a common point form a triradius which when located at or very near the proximal margin of the palm is in the t position (figure 4). Axial triradii located near the transverse flexion crease in the middle of the palm are in the t″ position, the most distal or highest position in which axial triradii are located. Axial triradii located in the intermediate area between t″ and t are called t′. The symbol 0 signifies absence of any axial triradius.

In none of the 10 hands of the 5 fully affected cases (table 6) was the highest axial triradius as low as the most common t position. In one person the highest position on each hand was t′ and in each of the remaining 8 hands the highest position was t″ which was 10 × the number expected according to the frequency distribution of 1,281 German males reported by Cummins and Midlo (1943). In their study the position of the most distal axial triradius appeared in the t, t′, or t″ position with a

TABLE 6.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND POSITION OF HIGHEST AXIAL TRIRADIUS

See figure 4 for illustration of position of axial triradius. Control values are from a study of 1281 German males reported by Cummins and Midlo (1943).

Highest Axial Triradius	Control	Syndrome		Carrier		Normal	
		Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
t″	8.3	8	.8	13	5.2	3	6.0
t′	28.0	2	2.8	21	17.3	12	20.1
t	62.9	0	6.3	26	39.0	57	43.3
0	.8	0	.1	2	.5	0	.6
Total	100.0	10	10.0	62	62.0	72	72.0

frequency of 62.9, 28.0 and 8.3 percent, respectively, and there was no triradius (0) in only 0.8 percent of the hands.

In 13 of the 62 hands of heterozygotes the highest triradial position was in the t″ position which is approximately 2.5 × the number expected. Three of the 72 hands of normal homozygous individuals had a triradius in the t″ position which is half the expected number and is not significant.

Cummins (1939) first noted the occurrence of t″ in the palms of mongoloids to be 8 times the frequency found in any known racial group and suggested that the position of the axial triradius might be a useful sign in the diagnosis of mongolism. We are indebted to this same author for first calling to our attention the high frequency of t″ in the palms of individuals possessing genes for the spherophakia-brachymorphia syndrome.

Penrose (1954) demonstrated the value of using the *atd* angle (fig. 4) in the study of mongolism. In a control population of 510 adult males and 507 adult females he reported the mean and standard deviation of the *atd* angles (based on the sum of the largest *atd* angle in the right and left hands): 85.04 ± 15.27° in males and 85.93 ± 15.70° in females. Corresponding values for lower age groups were found to be for 28 males 0–4 years of age 92.54 ± 14.15°, for 483 males 5–14 years of age 88.14 ± 15.86°, for 32 females 0–4 years of age 97.67 ± 19.64°, and 486 females 5–14 years of age 89.81 ± 17.27°, respectively.

As in stature large and very large *atd* angles may be defined to be from one to two, and two or more standard deviations above the mean, respectively. Large and very large *atd* angles would be expected to occur in approximately 1/7 and 1/44 individuals, respectively, selected at random from a normal population. In terms of the values found by Penrose a large *atd* angle would range in males from 100.32 to 115.57° and for females from 101.63 to 117.32°. Very large *atd* angles for males would be ≥115.58 and for females ≥117.33. The range, mean and standard deviation for size of *atd* angles in the various groups are given in table 7.

TABLE 7.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND SIZE OF *atd* ANGLE

The size of the *atd* angle used is the sum of the largest *atd* angle (figure 4) on the right and left palms. Control values are from Penrose (1954).

Group	Number	Sex	Range (degrees)	Mean and Standard Deviation
Syndrome	3	♂	119.0–128.5	124.8 ± 4.2
Syndrome	2	♀	145.5–158.5	152.0 ± 6.5
Syndrome	5	♂ and ♀	119.0–158.5	135.7 ± 14.3
Carrier	16	♂	77.0–147.9	103.5 ± 20.1
Carrier	12	♀	82.0–136.6	102.2 ± 20.5
Carrier	28	♂ and ♀	77.0–147.9	102.9 ± 20.3
Normal	14	♂	75.0– 89.0	80.5 ± 4.3
Normal	17	♀	76.5–118.0	90.8 ± 10.9
Normal	31	♂ and ♀	75.0–118.0	86.2 ± 10.0
Control	510	♂	55.0–160.0	85.0 ± 15.3
Control	507	♀	55.0–150.0	85.9 ± 15.7
Control	1017	♂ and ♀	55.0–160.0	85.5 ± 15.5

The *atd* angles of 3 adult males with spherophakia-brachymorphia ranged from 119 to 128.5° with a mean and standard deviation of 124.8 ± 4.2°. The corresponding values for two fully affected females ranged from 145.5 to 158.5° with a mean and standard deviation of 152.0 ± 6.5°. In every case the *atd* angle was very large with an occurrence 44 times the frequency expected in the general population (5 ÷ $^{5}/_{44}$).

The *atd* angles of 16 adult carrier males ranged from 77° to 147.9° with a mean and standard deviation of 103.5 ± 20.1. Among these 16 carrier males, 5 had very large *atd* angles (1-79, 1-154, and with age adjustments, 1-124, 1-165b, 2-27); with age adjustments 3 had large *atd* angles (1-159, 1-165d, and 1-188); 8 had average size *atd* angles (1-44, 1-58, 1-104, 1-153, 1-163, and with age adjustments 1-158, 1-185, 1-192). The values for 12 females ranged from 82 to 136.6° with a mean and standard deviation of 102.2 ± 20.5. Among these 12 carrier females, 2 had very large *atd* angles (1-100, and with age adjustment 1-157); 3 had large *atd* angles (1-83, 1-151, and 2-18); 7 had average size *atd* angles (1-66, 1-152, 1-161, 1-168, 2-15, 2-23, and with age adjustment 1-191). Very large *atd* angles occurred 11.0 × the frequency expected in the general population (7 ÷ $^{28}/_{44}$) and large or very large *atd* angles occurred 3.3 × the frequency expected in the general population (13 ÷ $^{28}/_{7}$).

The *atd* angles of 14 normal homozygous adult males ranged from 75 to 89° with a mean and standard deviation of 80.5 ± 4.3°. (These 14 males included 1-82, 1-84, 1-86, 1-99, 1-114b, 1-114c, 1-114d, 1-131a, 1-164b, 2-9, 2-12, 2-17 and with age adjustments 1-131b, and 1-137.) The values for 17 normal females ranged from 76.5 to 118° with a mean and standard deviation of 90.8 ± 10.9°. (These 17 females included 1-34, 1-69, 1-71, 1-77, 1-81, 1-85, 1-93, 1-114a, 1-119, 1-164a, 1-169, 2-16, 2-20, and with age adjustments 1-136, 1-160a, 1-164c and 1-193.) All 14 normal males had average size *atd* angles. Among the 17 normal females, one had very large (1-114a), two had large (1-85, and 1-119) and 14 had average size *atd* angles. Very large *atd* angles occurred 1.4 times the frequency expected in the general population (1 ÷ $^{31}/_{44}$) and large or very large *atd* angles occurred 0.7 times the frequency expected in the general population (3 ÷ $^{31}/_{7}$).

The mean and variances of various groups were compared with one another to determine whether or not differences between them were statistically significant. With few exceptions the t and F values summarized in table 8 were found to be similar to those obtained for stature.

The *atd* angles in individuals with the syndrome were larger in females than in males, but the size of these groups was too small for a valid statistical comparison (comparison 1). Likewise, when these two groups were used for comparisons 2, 3 and 4 they were too small to assure valid results, but if similar values were to be obtained with larger numbers one might conclude that the presence of two genes for the syndrome in contrast to one or none increases the size of *atd* angles (comparisons 3 and 4).

The larger *atd* angles observed in normal females than in normal males (comparison 9) were probably fortuitous since such a difference was not found among heterozygotes (comparison 5) or among the controls (comparison 16).

In contrast to the normal and control groups the presence of a single gene for spherophakia-brachymorphia seemed to increase the size of *atd* angles (comparisons 6,

TABLE 8.—VALUES OF t AND F OBTAINED FROM TESTS OF SIGNIFICANCE APPLIED TO DIFFERENCES OF *atd* ANGLES AND OF STANDARD DEVIATIONS AMONG THE VARIOUS GROUPS

Number	Groups Compared	Degrees Freedom ($n_1 + n_2 - 2$)	t-value	F-value
1	Syndrome ♂♂ and syndrome ♀♀	3	4.4*	3.2
2	Syndrome ♂♂ and carrier ♂♂	17	1.7	16.6
3	Syndrome ♀♀ and carrier ♀♀	12	3.2**	5.4
4	All syndromes and all carriers	31	3.4**	1.7
5	Carrier ♂♂ and carrier ♀♀	26	.2	1.1
6	Carrier ♂♂ and normal ♂♂	28	4.1**	21.4**
7	Carrier ♀♀ and normal ♀♀	27	1.9	3.7**
8	All carriers and all normals	57	4.0**	4.2**
9	Normal ♂♂ and normal ♀♀	29	3.2**	6.2**
10	Carrier ♂♂ and control ♂♂	524	4.7**	1.8*
11	Carrier ♀♀ and control ♀♀	517	3.5**	1.9*
12	All carriers and all controls	1043	5.8**	1.8**
13	Normal ♂♂ and control ♂♂	522	1.1	11.6**
14	Normal ♀♀ and control ♀♀	522	1.3	2.0*
15	All normals and all controls	1046	.1	2.3**
16	Control ♂♂ and control ♀♀	1015	.9	1.1

* .05 level of significance.
** .01 level of significance.

8, 10, 11, 12). The value obtained in comparison number 7 between heterozygous females and normal females was not statistically significant due possibly to (1) other genes or environmental factors causing large *atd* angles in these females, or (2) failure to detect heterozygotes who were falsely classified in the normal group.

The variance in *atd* angles as indicated by significant and highly significant F-values was larger in heterozygotes (males and females) than in the normal or control groups (comparisons 6, 7, 8, 10, 11, 12). The variance in normal males was less than that of control males (comparisons 13, 14, 15). This may be because males belonging to two kindreds were more homogeneous for genes not associated with the syndrome than individuals selected at random. The smaller variance in normal males than in normal females (comparison 9) must be fortuitous.

SPAN INDEX

Span index was obtained by dividing span by height and multiplying by 100. The range, mean, and standard deviation for the span index values in the various groups are listed in table 9, but the numbers of individuals in most of the groups are too small for statistical comparisons. The values for all individuals believed to carry one or two genes were reduced and this is in the direction expected if "shortened extremities" are also a stigma of the syndrome.

There was one statistically significant difference among the various groups. The mean and standard deviation for the span of all 5 affected individuals was 93.4 ± 3.1 and the corresponding values for all 15 carriers was 98.8 ± 3.2. The t-value for the difference in these two groups was 3.0 which with 18 degrees of freedom would be

TABLE 9.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND SPAN INDEX

Span index = (span × 100) ÷ stature.

Group	Number	Sex	Range	Mean and Standard Deviation
Syndrome	3	♂	89.0– 97.7	94.3 ± 3.8
Syndrome	2	♀	91.7– 92.4	92.0 ± .3
Syndrome	5	♂ and ♀	89.0– 97.7	93.4 ± 3.1
Carrier	8	♂	91.9–106.9	99.9 ± 4.0
Carrier	7	♀	94.1–100.8	98.8 ± 2.4
Carrier	15	♂ and ♀	91.9–106.9	98.8 ± 3.2
Normal	8	♂	98.0–106.7	101.6 ± 2.5
Normal	6	♀	95.0–104.0	99.0 ± 2.9
Normal	14	♂ and ♀	95.0–106.7	100.4 ± 3.0

expected less than once in 100 if the homozygous state of spherophakia-brachymorphia gene has no effect upon span index.

The importance to be attached to low span index for affected individuals is questionable since the value calculated from the data reported by Diethelm (1947) for an affected female was 100.3 and the value calculated from data reported by Stadlin and Klein (1948) for an affected female was 100.0. No control span index values were available to determine how much the values obtained deviate from the mean.

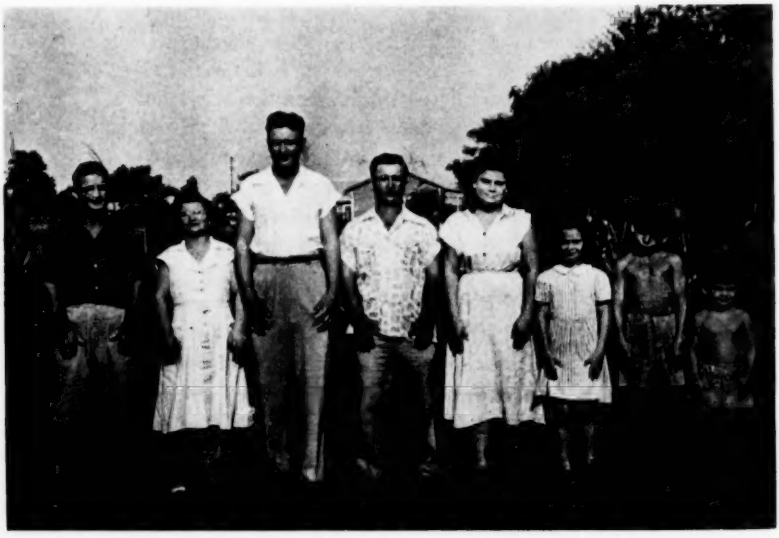

FIG. 5. Individuals in Kindred 1, from left to right are: 1-96, propositus who has recessive type of spherophakia-brachymorphia syndrome; 1-102, homozygous affected sister; 1-99, homozygous normal brother (5′8″ tall); 1-105, homozygous affected brother, 1-105w, homozygous normal wife of 1-105; 1-165c, 1-165b and 1-165d, heterozygous carrier children of 1-105 and 1-105w.

FIG. 6. Brachydactyly in an individual (pedigree number 1-94) who has recessive type of spherophakia-brachymorphia syndrome.

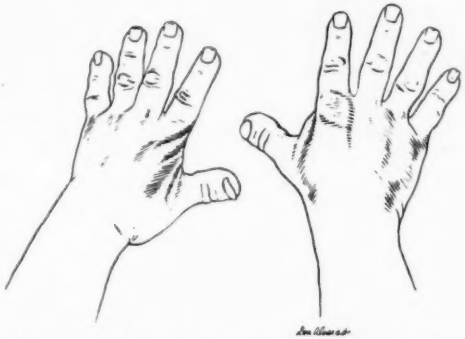

FIG. 7. Brachydactyly in an individual (pedigree number 2-19) who has recessive type of spherophakia-brachymorphia syndrome.

DISCUSSION

In the absence of specific anthropometric data, subjective ratings do not communicate the same impression to all readers. No one previously has attempted to indicate precisely the demarcation between "short" and "average." Deviations from a mean encountered in one out of 7 or one out of 44 from a random population are not particularly obvious. See figures 5–7 for photographs of fully affected individuals. The need of objective measurements is apparent if anthropometric data for various studies are to be combined.

The selection of deviations from the mean in the direction of the syndrome as small or smaller than one would expect to find in 1/9 (eye), 1/20 (stature), 1/7 (finger length) and 1/9 (*atd* angle) of a random population appears to be rather arbitrary but these stigmata do seem to separate 74 relatives of the 5 fully affected homozygotes into one group of 38 heterozygotes and another group of 36 normal homozygotes.

The values reported by Watson and Lowrey (1951) for stature were used as controls because they cover the lower age levels in both sexes. With the use of a control population more appropriate for American families of French descent in this region values deviating as much or more than those occurring in about one in 7 of the population would be equivalent to the one in 20 obtained when tables for stature based on the Iowa study were used. The mean stature of adult males from the areas in which our kindreds live, as reported by Davenport and Love (1921) for World War I enlistees, was 4.0 cm. shorter than the value given by Watson and Lowrey (1951); the Newman (1951) figure for World War II service men at discharge was 2.8 cm. shorter; and the Randall (1949) figure for similarly selected adult females was 3.2 cm. shorter.

The observed association between wide *atd* angle and the gene for spherophakia-brachymorphia might be explained in one of three ways: (1) A wide *atd* angle is one of the stigmata of the syndrome occurring more frequently in both homozygous affected and heterozygotes than in normal homozygotes. (2) A gene contributing to wide *atd* angle might exist and be located on the same pair of chromosomes as the gene for the syndrome. If these two genes were on the same chromosome in a large family in which most of the observations were made, both might tend to be present in the same individuals and to be absent in others. If this explanation be true one would not expect this association to occur in more than half of the families segregating for both the spherophakia-brachymorphia syndrome and wide *atd* angle depending upon the repulsion or coupling phase of the genes. (3) A third explanation is that the relationship between the syndrome and wide *atd* angle is fortuitous. The genetics of variation in the *atd* angle is unknown. We consider the first explanation the most plausible and thus have treated wide *atd* angle as a stigma of the syndrome.

The omission of wide *atd* angle as a stigma would have caused only four individuals (1-79, 1-83, 2-18, and 2-27) to have been left out of the group of 38 heterozygotes listed in tables 10 and 11. In like manner the omission of stigmata for stature, finger-palm index or eye departures in the direction of the syndrome would have caused 16, 12 or 2 respectively, to have been left out of the heterozygous group.

Among 74 observed relatives of the 5 fully affected individuals, 38 were heterozygous and 36 (used in calculations) were homozygous normal according to the criteria described previously for selection of heterozygotes. With one exception (1-80 who was 133.4 cm. tall, a height this short or shorter to be expected once in a million) the criteria were adhered to strictly in spite of the fact that specific information about one or more stigmata was lacking in many cases. In addition, 17 relatives were observed but precise measurements were not made. It is our opinion that among these 17 observed relatives, 3 were heterozygous (1-54, 1-165e, and 1-165f), 1 was homozygous normal (1-16), and 13 could not be classified (1-160b, 1-186e,

TABLE 10.—STIGMATA FOUND IN HETEROZYGOUS MALES

Stigma present, ×; stigma absent, 0; information about stigma missing, ? Column A represents assumed heterozygotes because they were (1) offspring or parents of fully affected homozygotes or (2) the parents of a heterozygous child and related to propositus. Column B represents heterozygotes who possessed two or more stigmata of the syndrome. Column C represents individuals who would have been placed in homozygous normal group had the particular stigma above the column not been observed. Final column gives approximated probability of encountering an individual in a random population with stigmata deviating as much or more in the direction of the syndrome if stigmata are uncorrelated within individuals.

Pedigree Number	Eye			Short Stature			Short Fingers			Wide *atd* Angle			Probability
	A	B	C	A	B	C	A	B	C	A	B	C	
1-26	0			×			×			?			7.1×10^{-3}
1-44		?			×	×		×	×		0		1.5×10^{-3}
1-58		0			×	×		×	×		0		4.2×10^{-3}
1-59		0			×			×			×		1.4×10^{-4}
1-64		?			×	×		×	×		0		5.5×10^{-4}
1-79		×	×		0			0			×	×	7.8×10^{-4}
1-104	?			×		×	0			0			2.0×10^{-3}
1-124		×			×			×			×		2.1×10^{-6}
1-140		?			×	×		×	×		?		5.5×10^{-4}
1-148	?			×		×	?			?			5.0×10^{-2}
1-153	0			×			×			0			4.0×10^{-4}
1-154	×			×			×			×			5.8×10^{-10}
1-158		0			×	×		×	×		0		8.6×10^{-4}
1-159		0			×			×			×		4.8×10^{-4}
1-163		?			×	×		×	×		0		1.3×10^{-3}
1-165b	×			×			×			×			1.0×10^{-9}
1-165d	0			×			×			×			4.2×10^{-7}
1-185		0			×	×		×	×		0		1.3×10^{-3}
1-188		×			×			?			×		9.9×10^{-5}
1-192		0			×	×		×	×		0		6.5×10^{-4}
2-27		0			×	×		?			×	×	1.1×10^{-3}
Total	2	3	1	7	13	11	5	11	8	3	6	2	
Percent	40.0	30.0	4.8	100.0	92.9	52.4	83.3	91.7	38.1	60.0	46.2	9.5	

1-186f, 1-186g, 1-189, and 1-190 who were 3 months to 3 years old; 1-48, 1-90, 1-108a, 1-108b, 1-186b, 1-186c, 1-186d who were over 3 years old).

Among 39 individuals who were not observed, 1-97 would have become fully affected according to relatives, 25 were probably heterozygous (1-1, 1-8, 1-10, 1-11, 1-12, 1-14, 1-17, 1-20, 1-23, 1-25, 1-28, 1-35, 1-37, 1-39, 1-41, 1-42, 1-47, 1-65a, 1-65b, 1-87, 1-91, 150a, 150b, 2-7, 2-8), and 13 were most likely homozygous normal (1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-15, 1-19, 1-36, 1-38, 1-51, 1-53, and 2-24) according to pedigree relationships and reported information. An additional 738 relatives were not observed or classified.

The authors are well aware that an association between two traits in an individual is no proof that the two traits are causally related to one another or to a third cause

TABLE 11.—STIGMATA FOUND IN HETEROZYGOUS FEMALES

Sitgma present, ×; stigma absent, 0; information about stigma missing, ? Column A represents assumed heterozygotes because they were (1) offspring or parents of fully affected homozygotes or (2) the parents of a heterozygous child and related to the propositus. Column B represents heterozygotes who possessed two or more stigmata of the syndrome. Column C represents individuals who would have been placed in homozygous normal group had the stigma above the column not been observed. Final Column gives approximated probability of encountering an individual in a random population with stigmata deviating as much or more in the direction of the syndrome if the stigmata are uncorrelated within individuals.

Pedigree Number	Eye			Short Stature			Short Fingers			Wide *atd* Angle			Probability
	A	B	C	A	B	C	A	B	C	A	B	C	
1-40		?			×	×		×	×		?		1.0×10^{-3}
1-66	0			×			×			0			1.9×10^{-6}
1-80		?			×	×		0			?		1.0×10^{-7}
1-83		×	×		?			0			×	×	9.0×10^{-4}
1-100	×			×			0			×			5.0×10^{-8}
1-109		?			×	×		×	×		?		2.3×10^{-6}
1-151	×			×			0			×			1.1×10^{-6}
1-152	×			×			×			0			2.3×10^{-4}
1-157		×			×			0			×		1.0×10^{-7}
1-161	×			×			0			0			7.4×10^{-4}
1-165a	0			×			×			?			7.1×10^{-3}
1-165c	0			×			×			?			7.1×10^{-3}
1-168	0			0			×		×	0			1.5×10^{-3}
1-191		0			×	×		×	×		0		1.4×10^{-3}
2-15	0			×			×			0			1.3×10^{-6}
2-18		0			×	×		0			×	×	3.3×10^{-3}
2-23	×			×			0			0			7.4×10^{-4}
Total	5	2	1	9	6	5	6	3	4	2	3	2	
Percent	50.1	50.0	5.9	90.0	100	29.4	60.0	42.9	23.5	25.0	75.0	11.8	

(gene). Yet, when short stature and short fingers have been observed to be associated with the eye condition described in the spherophakia-brachymorphia syndrome on so many different occasions the most plausible explanation is that some common gene is causing both traits even though genes at various loci are believed to contribute normally to these variations. One would expect the effects of the gene in spherophakia-brachymorphia to vary according to the presence of genes normally contributing to variation in these traits. This same generalization might be made for the values obtained for the other stigmata. However, unless associations between these stigmata occur in the general population (no significant correlation was found between finger-palm index and stature), one would not expect to find so many constellations of these stigmata in so many individuals chosen from a random population.

Tables 10, 11, and 12 give the frequencies of stigmata in heterozygous males and females and of the particular combinations observed in the various individuals. Had data been complete in every case for all 4 stigmata, many of the probabilities of

TABLE 12.—FREQUENCY* OF STIGMATA IN HETEROZYGOTES

The stigmata represented in the first column are eye departures in the direction of the spherophakia-brachymorphia syndrome, short stature, short fingers and wide *atd* angle.

Stigma	Males			Females			Males and Females		
	Number	Number with stigma	Percent with stigma	Number	Number with stigma	Percent with stigma	Number	Number with stigma	Percent with stigma
Eye	16	5	31.3	14	7	50.0	30	12	40.0
Stature	26	24	92.3	22	20	90.9	48	44	91.7
Fingers	18	16	88.9	17	9	52.9	35	25	71.4
atd angle	19	9	47.4	12	5	41.7	31	14	45.2

* Exclusive of duplications the individuals used in the preparation of this table include those used in the derivation of statistical values and those listed in tables 10 and 11.

encountering at random such a group of stigmata in the direction of the syndrome would undoubtedly be higher, and perhaps some classed as normal in Tables 13–14 would need to be transferred to the heterozygous group. So many high values for these probabilities even when adjustments are made for a more adequate control population suggest that something other than chance must have caused the stigmata to be present in these particular relatives. Had time permitted examination of relatives in other branches of the kindreds, many more heterozygous carriers would undoubtedly have been found. In most cases the selection of particular branches for study was dependent upon proximity of individuals to the examiners. Since most cases thought by relatives to be deviating to an extreme degree in the direction of the syndrome were checked, other cases of the full syndrome are not considered to occur in these two kindreds, although there is good reason to believe from reports by relatives that had 1-97 lived, he too would have had the full syndrome for he had brachydactyly as extreme as any of his fully affected siblings.

Short stature, short fingers, wide *atd* angle, and eye abnormalities in the direction of the syndrome were present in all 5 fully affected individuals and they occurred in 91.7, 71.4, 45.2 and 40.0 percent of the heterozygotes, respectively (table 12). These values are also estimates of penetrance for the spherophakia-brachymorphia gene.

The possibility of error in classification of a heterozygote is believed to be about 10%. It should be emphasized that it may not be correct statistically to include individuals in the calculation of penetrance values who were placed in the group because they possessed a particular stigma. When these individuals are omitted (3, 27, 12, and 5 individuals, respectively, for each of the foregoing stigmata), estimates of penetrance become 90.5, 56.5, 38.5, and 37.0 percent. These values do not differ significantly from the preceding estimates.

Since 1 out of 12 assumed heterozygotes (1-168) who were examined for all 4 stigmata possessed only one stigma, it is possible that the standards used for selection of heterozygotes were too severe and some who possess a single stigma and were classed as homozygous normals should be considered heterozygous. The two in the normal group with the lowest probabilities were 2-9 and 2-17. However, it was felt better to err on the conservative side, and except for assumed heterozygotes and 1-80, the presence of two stigmata was considered necessary to identify a heterozygote.

Stigmata were present in the following combinations in the group of 17 assumed heterozygotes listed in tables 10 and 11: 2 had short stature only (information was lacking in one or three stigmata); 6 had short stature and short fingers (3 lacked information in one stigma); 2 had short stature and eye departures, one had eye departures and wide *atd* angle (information lacking in one stigma); 2 had short stature, eye departures, and wide *atd* angle; one had short stature, short fingers and wide *atd* angles; one had short stature, eye departures, and short fingers; and 2 had all 4 stigmata.

In the group of 21 heterozygotes who possessed two or more stigmata the following combinations were present: 11 possessed short stature and short fingers (6 lacked information for one or two stigmata); two possessed eye abnormalities and wide *atd* angles (one lacked information in one stigma); two possessed short stature and wide *atd* angles (1 lacked information in one stigma); two had eye abnormalities, short stature, and wide *atd* angles (1 lacked information about finger-palm index); two had short stature, short fingers and wide *atd* angles; one had all 4 stigmata; and one (information not known in two stigmata) had an extremely short stature only.

Undoubtedly there are many other stigmata associated with this syndrome in addition to the 4 described in this study. Further study should be given to the stiffness of phalangeal joints and the stiffness of lower limb joints which is present in some affected individuals. The stiffness of the lower limb joints may account for the peculiar walk observed in 1-96, reported by relatives in 1-14, 1-41, 1-165f, and also described in a case by Stadlin and Klein (1948).

Anthropometric values in all 5 individuals with the full syndrome and in 20 to 29 individuals who are normal homozygotes or carriers may be combined with additional data and reported later for the following: sitting height, weight, chest circumference, head height, height of trochlear point, height of anterior superior spine, upper arm length, forearm length, hand length, hand width, femur length, tibia length, ear length, ear width, ear lobes, hair color, handedness, presence of midphalangeal hair, ability to curl tongue, ability to taste P.T.C., direction of hair whorl, ABO, MN, and Rh blood types. Also, palm and finger prints were taken on all individuals in which the size of the *atd* angle is reported. The anthropometric values reported by Diethelm (1947) make a fine model to be followed when anthropometric values are to be obtained in a study of spherophakia-brachymorphia.

Notations were made about the presence of three additional rare traits segregating in these two kindreds. A very large thumb was noted bilaterally in 2-9, 2-19 and 2-20, and a tendency to develop gout was present in 2-7, 2-18 and 2-25a. One or two genes for schizophrenia are believed to be present in the following individuals: 1-10, 1-16, 1-21, 1-23, 1-35, 1-39, 1-47, 1-60e, 1-80, 1-90, 1-109 and 1-146a. Had information about schizophrenia been sought, more individuals with one or two genes for schizophrenia undoubtedly would have been found.

SUMMARY

Two large kindreds, one containing 824 individuals of French descent and the other containing 49 individuals of Italian descent, are presented. Direct observations were made in 96 individuals.

Criteria are presented which were found useful to distinguish 38 heterozygous carriers of the spherophakia-brachymorphia gene from 36 homozygous normals and 5 homozygous affected individuals. With the exception of 17 individuals (8 under 3 years old) information was sufficient to classify all persons observed. Four of these 17 could be placed in heterozygous or normal groups from pedigree relationship and subjective impressions.

Anthropometric stigmata which were found most useful to distinguish the various genotypic groups were short stature, short fingers, and wide *atd* angles.

Range, mean and standard deviation are given for each stigma in each genotypic group, and separately for each sex.

Tests of significance are reported which show that the values obtained for the various groups are statistically significant in spite of the small numbers of individuals in some of the groups.

The penetrance of the gene for the spherophakia-brachymorphia syndrome in heterozygous carriers was found to be 91.7, 71.4, 45.2 and 40.0 percent for short stature, short fingers, wide *atd* angle, and ocular departures from normal in the direction of the syndrome, respectively. In homozygous affected individuals penetrance was 100% for each of these four stigmata.

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APPENDIX

TABLE 13.—DATA FOR INDIVIDUALS IN SPHEROPHAKIA-BRACHYMORPHIA KINDREDS REPRESENTED BY PEDIGREES 1 AND 2

In bilateral observations the value for the right eye or hand appears first. In column under "Classification" the first four digits refer respectively to eye, stature, finger-palm index and *atd* angle. In each of these the status of the stigma is identified by numerals as follows: 1, stigma present; 2, stigma absent; 3, undetermined. The fifth digits indicate: 1—heterozygous carrier (partial syndrome), 2—homozygous normal, 3—undetermined, and 4—homozygous affected (full syndrome). For explanation of stigmata see "Criteria used in selection of heterozygotes."

Pedigree Number	Age	Sex	Visual Acuity Without Glasses (except with c̄)	Fundi Seen With	Stature (cm)	Span (cm)	Finger Length (mm)					Palm Width (mm)	t-tri-radius	*atd* Angle (°)	Classification
							I	II	III	IV	V				
1-34	65	♀					44	76	81	75	56	90	t	43.0	33222
							60	76	79	75	59	87	t	40.5	
1-40	65	♀			153?		54	64	72	67	52	85			31131
							51	64	72	68	52	84			
1-44	55	♂			165.1		57	67	75	72	54	92	t	37.5	31121
							55	67	78	75	56	93	t	38	
1-45	60	♀			av.		51	70	76	71	55	85	t		32232
							51	71	74	72	53	88	t		
1-58	61	♂	20/15c̄	+1	152?		47	63	73	69	55	88	t	40.5	21121
			20/15c̄				48	68	77	71	56	87	t	45.5	
1-66	46	♀	20/40		144?		48	61	68	65	43	82	t	42.5	21121
			20/20				48	63	70	64	45	79	t	45.0	
1-69	26	♀	20/70	−3	av.		53	73	82	72	58	79	t	38.5	12222
			20/50				55	72	81	74	57	79	t′	44.5	
1-71	43	♀	20/40		160.6		59	71	80	73	53	81	t	42.5	22222
			20/40				58	68	80	73	53	79	t	45.0	
1-77	50	♀	20/200				52	70	80	76	60	88	t	43.5	23222
			20/200				52	72	80	75	58	86	t	43.5	
1-79	55	♂	20/200	−1	177.8?		60	91	100	93	69	99	tt″	76.5	12211
			L.P.				63	84	94	92	72	104	t	46.5	
1-80	49	♀			133.4		47	61	72	69	56	79			31231
							46	62	69	69	79				
1-81	51	♀	20/200	+6			53	71	81	79	61	90	t	38.0	23222
			20/200				55	73	81	79	60	89	t	38.5	
1-82	40	♂	20/20c̄	+2			60	75	85	81	65	99	t	40.5	23222
			20/20c̄				57	79	90	83	66	98	t	37.0	
1-83	43	♀	20/30c̄	−2			51	78	87	79	60	89	0		13211
			20/20c̄				57	74	85	78	59	88	t′	53.5	
1-84	38	♂	20/200	+3	av.		57	72	81	78	61	98	t	38.5	22122
			20/200				54	72	80	77	62	100	t	36.5	
1-85	34	♀	20/15	0	av.		55	70	78	74	58	85	t	40.5	22212
			20/15				51	70	77	71	56	83	tt″	71.0	
1-86	56	♂	20/30				51	71	78	78	58	97	t	36.5	23122
			20/30				56	69	77	75	58	96	t′	40.5	
1-93	50	♀					56	74	81	74	55	85	t	46.5	33222
							49	74	81	73	55	88	t	44.5	
1-94	49	♀			140.7	130.0	42	46	55	57	42	80	t″	74.0	11114
							40	42	53	56	40	82	t″	71.5	
1-96	47	♂			151.1	134.5	41	46	53	60	45	87	t″	66.5	11114
							47	48	57	58	43	87	tt″	60.5	

TABLE 13.—*Cont.*

Pedigree Number	Age	Sex	Visual Acuity Without Glasses (except with ♂)	Fundi Seen With	Stature (cm)	Span (cm)	Finger Length (mm)					Palm Width (mm)	t-triradius	*atd* Angle (°)	Classification
							I	II	III	IV	V				
1-99	28	♂	20/20	−4	173.5	172.5	58	73	82	76	61	94	t	40.5	12222
			20/20				58	72	82	76	60	92	t	42.0	
1-100	46	♀	20/70	−6	154.4	154.0	55	70	80	78	55	86	tt″	77.5	11211
			20/70				60	68	77	75	57	82	tt″	72.5	
1-102	41	♀			137.4	126.0	45	43	46	48	42	83	t″	80.5	11114
							41	45	50	52	39	82	t″	78.0	
1-104	42	♂			159.9	171.0	58	74	83	76	61	94	t	37.0	31221
							63	76	84	78	61	90	t′	40.0	
1-105	33	♂			153.0	147.0	48	58	67	66	52	96	tt″	68.0	11114
							56	63	69	67	51	91	tt″	60.5	
1-109	26	♀			142?								t		31111
							41	57	67	60	44	75	t″		
1-114a	24	♀	20/25	0	166.4	173.0	61	82	92	87	68	94	tt″	55.5	22212
			20/20				61	84	92	86	67	92	tt″	62.5	
1-114b	22	♂	20/20	0	176.0	172.5	60	76	86	80	62	100	t	40.0	22122
			20/20				60	80	82	70	54	100	t	41.0	
1-114c	18	♂	20/20	0	175.8	178.0	62	87	93	87	70	104	t	42.0	22222
			20/20				59	85	92	87	67	107	t	43.0	
1-114d	17	♂			173.4	177.0	67	80	87	81	61	97	t	40.0	22222
							62	82	88	80	63	97	t	43.5	
1-119	42	♀	20/200	0									t′	54.0	23312
			20/20										t′	51.0	
1-124	13	♂	20/30	−3	short		51	58	69	64	45	83	tt″	80.5	11111
			20/40				51	58	68	65	44	81	t	45.5	
1-131a	20	♂	20/15	0	tall		64	83	94	87	69	93	t′	48.0	22222
			20/15				60	85	96	89	70	92	t	38.0	
1-131b	14	♂	20/15	0	aver.?		62	80	85	80	60	93	t	38.5	22222
			20/15				62	81	88	81	64	93	t	39.0	
1-136	11	♀	20/200	−6			52	63	69	66	51	79	t	41.5	13222
			20/200	−15			53	65	70	65	52	72	t	47.5	
1-137	9	♂	20/40				43	54	60	58	46	73	t	39.5	23222
			20/40				47	57	62	59	47	70	t	38.5	
1-151	24	♀	20/30	−3	148.5	139.8	46	65	71	68	52	75	t′	49.5	11211
			20/30				45	66	71	66	50	75	t′	55.5	
1-152	22	♀	20/25	−2	156.6	152.3	46	62	70	66	45	84	t	43.0	11121
			20/70				47	63	70	67	45	81	t′	56.0	
1-153	15	♂	20/20	0	153.1	155.2	49	68	77	73	51	92	0		21121
			20/20				52	70	80	73	54	91	t′	50.0	
1-154	15	♂	20/70	−	156.2	143.5	48	66	75	74	56	94	tt′	58.5	11111
			20/100				48	66	75	72	54	91	t″	69.0	
1-157	12	♀	20/70	−5			46	53	65	59	44	72	t″	69.0	11211
			20/30	−3	136.2?		51	55	66	59	44	73	t″	71.5	
1-158	10½	♂			128.7?		47	52	61	58	43	72	tt″	63.0	21121
							49	54	61	57	43	72	t	37.5	
1-159	5½	♂			106.7		41	50	58	53	40	66	tt″	62.0	21111
							45	48	57	53	39	67	t	49.5	
1-160a	4½	♀					37	50	58	53	43	63	t	50.0	23222
							37	51	56	54	42	62	t	54.0	
1-160b	3	♀											t′	62.0	23313
													t′t′	63.0	

TABLE 13.—*Cont.*

Pedigree Number	Age	Sex	Visual Acuity Without Glasses (except with c)	Fundi Seen With	Stature (cm)	Span (cm)	Finger Length (mm)					Palm Width (mm)	t-triradius	*atd* Angle (°)	Classification
							I	II	III	IV	V				
1-161	24	♀		−3	152.8		46	67	74	71	51	77	t′	53.0	11221
							49	66	74	70	53	81	t	39.5	
1-163	15	♂			163.0	162.5	57	71	80	75	54	93	tt′t′	45.5	31121
							60	70	79	74	53	92	t′	43.0	
1-164a	18	♀			152.0	153.0	50	66	74	68	51	82	t	41	31222
							49	65	75	75	51	81	t	41.0	
1-164b	17	♂			168.0	174.5	61	76	83	75	58	94	t	38.0	32222
							58	80	86	77	60	94	t	40.5	
1-164c	9½	♀			129.0	124.5	49	59	67	61	49	73	t	46.0	32222
							47	56	64	58	45	71	t	44	
1-165b	12⅓	♂	20/40		129.0	126.0	49	57	65	61	44	83	t″	74.0	11111
			20/70				54	59	64	61	45	81	t″	77.0	
1-165d	5	♂			very		30	43	50	46	33	68	t′	60.0	21111
					short		33	46	51	47	34	65	t′	59.0	
1-168	25	♀	20/25c	0	159.0	155.5	49	65	73	68	48	91	tt′	49.0	22121
			20/25c				50	65	74	68	51	89	t	43.0	
1-169	19	♀			163.9	162.5	50	65	76	70	53	85	t′	41.5	22222
							51	66	76	71	50	85	t′	46.5	
1-185	11	♂	20/20	0	133.3?		39	52	61	55	40	72	t	43.5	21121
			20/20				40	53	59	54	37	70	t	42.0	
1-186a	10	♂					46	57	67	61	44	74			23232
							51	60	67	61	47	74			
1-188	5½	♂	20/25	−1	105.9	103.2							t	47	11311
			20/20										tt′	61.5	
1-191	9	♀	20/50c	+6	123.1		40	54	58	54	39	68	t	43	21121
			20/60c				40	52	58	52	38	65	t	43.5	
1-192	8	♂	20/100c		121.8	118.3	38	52	57	54	41	70	t	44.0	21121
			20/40c				40	50	55	51	36	70	t	43.5	
1-193	4⅓	♀	20/30c		103.7		35	46	52	48	31	60	t′	42.5	22122
			20/20c				34	47	52	48	33	58	t′	45.5	
2-9	76	♂	10′		159.0	159.0	60	75	85	79	60	95	t	42.0	21222
			10′				59	67	82	76	56	92	t	40.0	
2-12	58	♂	L.P.		166.5	168.5	56	70	79	72	57	87	tt′	50	21222
			no L.P.				61	69	80	73	56	88	t	39	
2-15	54	♀	20/50		138.8	139.5	50	60	72	69	55	87	t	40.5	21121
			20/25				50	62	71	66	52	81	t	41.5	
2-16	51	♀	20/20	0	159.3	151.3	47	67	74	70	51	82	t	44.0	22222
			20/20				50	66	73	68	53	82	t	43.5	
2-17	48	♂	20/20	0	161.2	172.0	66	74	87	84	63	97	t	38.0	21222
			20/20				61	73	85	83	64	97	t	43.0	
2-18	46	♀	20/20	0	155.5	157.3	57	71	79	73	56	89	t′	48.5	21211
			20/20				58	72	78	71	55	87	t′	59.5	
2-19	40	♂			155.0	151.5	48	70	81	73	56	96	t′	57.0	11114
							51	72	80	73	56	94	t′	62.0	
2-20	51	♀	20/40		156.5	154.0							t	44.5	21322
			20/30										t	43.5	
2-23	28	♀	20/25	−1	152.2	153.5	51	64	74	68	56	80	t	37.5	11221
			20/40				51	62	74	68	55	80	t	46.5	
2-27	31⅓	♂	20/30	0	92.6	91.5							t′	50.5	21311
			20/20										t′	72	

TABLE 14.—REPORTED INFORMATION ABOUT RELATIVES OF INDIVIDUALS WITH THE SPHEROPHAKIA-BRACHYMORPHIA SYNDROME WHO WERE NOT AVAILABLE OR WHO WERE TOO YOUNG FOR COMPLETE EXAMINATION

* Indicates age at death. In column under "Possible Classification" the first four digits refer respectively to eye, stature, finger-palm index and *atd* angle. In each of these the status of the stigma is identified by numerals as follows: 1, stigma present; 2, stigma absent; 3, undetermined. The fifth digits indicate: 1—heterozygote, 2—homozygous normal, 3—undetermined, and 4—homozygous affected.

Pedigree No.	Age	Sex	Possible Classification	Remarks
1-9a	45*	♂	33133	
1-10	77*	♀	31131	Schizophrenia
1-11	d	♀	31331	
1-12	85*	♀	31131	
1-14	d	♀	31131	Peculiar walk
1-15	d	♂	32332	
1-16	90	♀	32222	t, t; schizoid
1-19	86*	♂	32332	
1-22	d	♀	33333	Blind
1-23	54*	♂	33331	Schizophrenia
1-25	70*	♂	31131	
1-26	76	♂	21131	O.U. 20/40s, early cataracts, glaucoma? t′, t′
1-27	70	♀	32333	
1-28	72	♀	31131	Blind
1-29	68	♂	21222	O.D. 20/20, O.S. 20/30; t, t
1-30	76	♀	32233	Long palms
1-35	67*	♂	32331	
1-36	60*	♀	32332	
1-37	60*	♂	31331	
1-39	d	♂	33131	
1-41	62*	♂	31131	Peculiar walk
1-42	52*	♀	31231	
1-47	50?	♂	32231	Schizophrenia
1-48	46	♂	32233	
1-50	72*	♂	32233	Long palms
1-51	70	♀	32332	
1-54	69	♂	21121	O.U. 20/200s; O.D. aphakia; O.S. mature cataract; t, t
1-59	47	♂	21111	t′, t″
1-64	32	♂	31121	t, t
1-65				Of 6 sibs 2 are 31133 and 4 are 33333
1-87	d	♀	31131	
1-90	47	♀	31233	
1-91	57	♂	31131	
1-95	43	♂	33333	
1-97	2*	♂	33134	Extreme brachydactyly
1-98	39	♂	33333	
1-101	7*	♂	33333	
1-103	39	♀	33333	
1-108a	32	♀	32233	
1-108b	30	♂	31223	

TABLE 14.—*Cont.*

Pedigree No.	Age	Sex	Possible Classification	Remarks
1-138	6	♂	22222	O.D. 20/30s̄; O.S. 20/20s̄; t, t
1-140	38	♂	31131	
1-144	27	♂	22222	O.U. 20/15; t, t
1-148	34	♂	31231	
1-150a	1 da*	♀	33331	
1-150b	1 da*	♀	33331	
1-165a	14	♀	21131	O.U. 20/20
1-165c	10	♀	21131	O.U. 20/45
1-165e	3	♂	33331	
1-165f	1	♂	33331	
1-186b–g			33333	3 boys and 3 girls ages 1–8
1-189	3	♀	33333	
1-190	1	♂	33333	

The Incidence of Cousin Marriages in a West-Swedish Rural Community

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THE COLLECTION OF DATA on consanguineous marriages for different regions is important from the point of view of population genetics. As one aspect of marriage customs, it should also interest cultural anthropology.

In Sweden, cousin marriages are not officially registered. Data may be obtained by interviews or objective genealogic investigations. However, interviews are of limited value even if one has secured a random sample of marriages. Hence in this work, as well as in a previous one (Böök 1948) and in those under way, we have used the latter method, although it requires a large amount of work.

AREA AND POPULATION

For this investigation, we have selected the rural community (or parish) of Östmark, located in the County of Värmland in middle West-Sweden (cf. fig. 1). The total area is 397 sq. km. of which 16 sq. km. are lakes or rivers. Only about 20 per cent of the area is cultivated, the remainder being forest. The original settlements were made during the thirteenth century by settlers of Swedish stock. Later, during the seventeenth century, a substantial immigration of people of Finnish stock took place. Thus in 1841, the total population was 3,800, of which 1,400 were registered as Swedes and 2,400 as Finns. The previous hostility between these two groups has eventually been straightened out. As late as one hundred years ago, there was only one by-road in the region. Overpopulation and poverty were characteristic features during earlier periods, which resulted in an emigration of over 2,000 people to the United States. Insufficient communications and relative geographic barriers have made the area very isolated and most of the small villages in the periphery obtained road connections only some 15 or 20 years ago. Out-migration to other parts of Sweden also contributed to the reduction of the population from a maximum of 5,326 in 1861 to a minimum of 2,862 in 1950. During the same period, the average number of children per family has decreased.

Table 1 shows the average population during 1900–50 and in- and out-migration rates per 1,000. It should be noted that the migration rates actually show only the general mobility of the population. So *e.g.* many, perhaps most, immigrants are former residents of the area who were born there. The general mobility of this population appears similar to the different North-Swedish isolates studied by Sjögren 1932 and 1935, and Böök 1953 (cf. Böök 1953).

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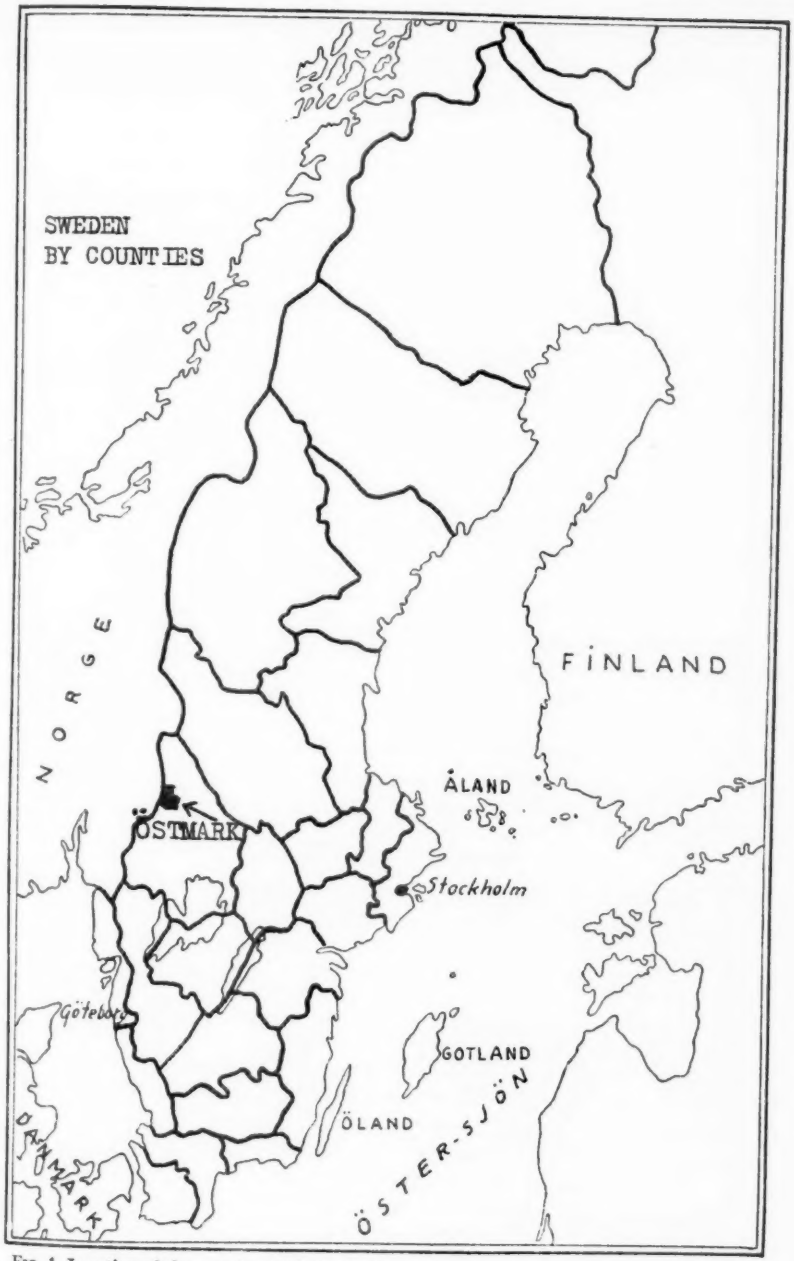

FIG. 1. Location of the area in which the incidence of first cousin marriages was determined

TABLE 1.—PARISH OF ÖSTMARK. AVERAGE POPULATION 1900–50 AND CRUDE MIGRATION RATES

Year	Average Population	Immigration Per 1,000	Outmigration per Year
1901–10	4,148	13	32
1911–20	3,856	13	27
1921–30	3,716	17	31
1931–40	3,419	21	37
1941–50	3,046	50	34

TABLE 2.—PARISH OF ÖSTMARK. THE FREQUENCY OF FIRST COUSIN MARRIAGES ACCORDING TO THE CENSUS 1925 AND 1954

Year	No. of 1st cousin marriages	Contracted during	Total No. of marriages	Per cent 1st cousin marriage
1925	7	1905–25	570	1.2
1954	7	1910–41	535	1.3

The above features of this rural population indicate that it should be regarded primarily as a geographic isolate.

THE FREQUENCY OF FIRST COUSIN MARRIAGES

We have made two census studies which measure the incidence of first cousin marriages among all existing marriages with both partners living. Table 2 shows the result. The time period between the censuses is approximately one generation. No appreciable change has occurred.

One of us (Måwe) made extensive sociologic investigation in this area and found a certain reluctance against cousin marriages, even if there was no actual discrimination.

EFFECTIVE POPULATION SIZE

As we are concerned here with a decreasing population, the actually breeding group may be estimated according to the formula

$$\frac{2b(b-1)f}{c_i} = N_i \qquad (1)$$

where b is the average number of children per family who grow up and marry within the area, f the frequency of fertile marriages, c_i the incidence of first cousin marriages, and N_i the effective population size at the corresponding period of time. A full discussion of such estimates will be published elsewhere (Böök, 1955).

For b equalling 2.0 and 1.5 respectively, f 0.95 and c_i 0.0125, the effective population size 1925–54 should be between 100 and 300 individuals. It is probably closer to the lower figure, as the reduction in size of the total population during this period has been substantial.

This estimate, which, of course is rather crude, appears to show that, in spite of

modern civilization and technical developments, there are still rural communities in Sweden where the actually-breeding groups have remained quite small.

SUMMARY

At cross-section investigations by the genealogic method, the incidence of first cousin marriages in a Middle West rural community in Sweden (population 2,862 in 1950) was determined at 1.2 per cent in 1925 and 1.3 per cent in 1954. The effective population size was estimated at 100–300.

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Data on the Etiology of Acute Intussusception in Childhood

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ACUTE INTUSSUSCEPTION in infancy and childhood is a condition of considerable clinical importance. Little is known of its etiology however; most of the relevant data have been obtained in the course of clinical investigation, and are unsuitable for examination of matters such as incidence, and its association with maternal age and birth order. An attempt was therefore made to assemble records of all infants and children in a large city who were treated for intussusception during a specified period. Data on all births in the same city were available from central records and from a $\frac{1}{200}$th sample which has been fully described elsewhere (Record and McKeown, 1949).

MATERIAL

Survey of the records of all pediatric and general hospitals in the City of Birmingham, England, for the years 1945–54 revealed 296 confirmed cases of intussusception in Birmingham children under the age of ten years. (An additional 103 patients treated in Birmingham hospitals but resident outside the city boundary have not been included.) 230 of the 296 Birmingham children were treated in the Birmingham Children's Hospital and the remainder in general hospitals. The diagnosis was accepted only if confirmed at operation. Ten cases (7 male, 3 female) in which laparotomy revealed evidence of spontaneous reduction of a previously existing intussusception were included, but instances of supposed spontaneous reduction without laparotomy were not.

The type of intussusception was stated in the operation notes of 254 patients. 214 (84.3%) were of the ileo-caecal* or ileo-colic* variety and 31 (12.2%) were ileo-ileal. The remainder were colo-colic (7) and multiple (2). This distribution is similar to that noted in previous reports (Koch and Oerum, 1912; Close, 1931; Wakeley and Atkinson, 1938; Gross and Ware, 1948; Wansbrough and Cram, 1952).

The presence of a "leading point" to the intussusception was noted in only four cases—two of Meckels diverticulum (males, aged 3 months and 8 months), one of colonic polyp (male, aged 4½ years) and one of jejunal polyp (male, aged 2 years). It is of course well recognised that acute intussusception in childhood can only rarely be attributed to such manifest local abnormalities (Koch and Oerum, 1912; Gross and Ware, 1948). In the present material one ileo-ileal intussusception in a boy aged 7 years was attributed to Henoch's purpura. There were three instances of recurrence, 3 months, 6 months and 2 years after the original operation. The last

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* No attempt is made to distinguish these two varieties since the criteria for their distinction are almost certainly not interpreted uniformly, and the difference between them is probably one of degree or duration rather than of etiology.

TABLE 1.—INCIDENCE OF INTUSSUSCEPTION IN BIRMINGHAM, 1945–54

Years	Number of Livebirths	Number Affected	Incidence (per 1000 live births)
1945–46	41,319	44	1.06
1947–48	44,530	46	1.03
1949–50	38,500	62	1.61
1951–52	36,955	75	2.03
1953–54	36,846	69	1.87
Total	198,150	296	1.49

case recurred for a second time 9 months after the second operation, an ileo-caecal intussusception being found on each occasion.

Information used in the following tables was obtained from three sources: (1) the hospital record (all cases); (2) interviews with the mothers during the year 1955 (212 cases); (3) the certificate of birth, obtained in the case of 30 patients who could not be traced in 1955. There remain 54 patients for whom information is limited to that recorded at the original hospital admission.

INCIDENCE

The numbers of patients with intussusception and the numbers of related livebirths are shown in Table 1. The incidence of intussusception was lower in the early years of this study than in the later years, but this observation may result from improved ascertainment. The total incidence for the ten year period (1.49 per thousand live-births*) is considerably lower than the only other estimate of incidence; Spence and Court (1950) found 127 cases among 33,600 births (3.8 per thousand births) in Newcastle-on-Tyne in the years 1944–49. In the Newcastle material there was also a marked secular trend, 31 per cent of the cases falling in the first three year and 69 per cent in the last three.

AGE AND SEX

Distribution of the patients according to age, sex and type of intussusception is given in Table 2. The sex ratio (65.2% male) agrees closely with most previous estimates, for example 68% (Fitzwilliams, 1908; Koch and Oerum, 1912; Perrin and Lindsay, 1921), 64.4% (Hipsley, 1935), 63.9% (Close, 1931), and 63.8% (Wansbrough and Cram, 1952).

65.2% of the patients were under one year of age. This is in agreement with reports of representative material (Koch and Oerum, 1912; Perrin and Lindsay, 1921; Close, 1931) although data from pediatric or babies' hospitals (Hogg and Donovan, 1946; Wansbrough and Cram, 1952) naturally show a higher proportion of patients under 1 year. The distribution by month within the first year is fairly typical, although most reports suggest that the highest incidence is slightly later, for example

* It is not strictly correct to refer the number of cases of intussusception to the number of births in the period, since, of course, some of the older patients were born outside the period. Since 65% of the patients were under one year, however, the error is not large when a ten year period is used, and is certainly less than that involved in exclusion of patients not born within the period.

TABLE 2.—DISTRIBUTION ACCORDING TO SEX, AGE AND TYPE OF INTUSSUSCEPTION

Age at Operation (months)	Ileo-colic*			Ileo-ileal			Other			Unknown			Total		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
0–	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	1	—	1	—	—	—	—	—	—	—	—	—	1	—	1
2	1	3	4	—	1	1	—	—	—	—	1	1	1	5	6
3	10	11	21	—	1	1	1	1	2	3	1	4	14	14	28
4	14	17	31	2	—	2	1	—	1	3	—	3	20	17	37
5	13	9	22	1	1	2	—	—	—	4	1	5	18	11	29
6	11	9	20	—	—	—	—	—	—	4	2	6	15	11	26
7	7	7	14	1	—	1	—	—	—	3	1	4	11	8	19
8	10	8	18	—	—	—	—	—	—	2	—	2	12	8	20
9	4	1	5	2	1	3	1	—	1	2	—	2	9	2	11
10	4	2	6	1	—	1	1	—	1	1	1	2	7	3	10
11	4	—	4	1	—	1	—	—	—	1	—	1	6	—	6
12–	21	9	30	2	—	2	—	—	—	5	1	6	28	10	38
24–	17	3	20	6	2	8	1	—	1	2	—	2	26	5	31
36 and over	12	6	18	8	1	9	3	—	3	2	2	4	25	9	34
Total	129	85	214	24	7	31	8	1	9	32	10	42	193	103	296

* Includes ileo-caecal.

TABLE 3.—SEX RATIO (PER CENT MALE) ACCORDING TO AGE AND TYPE OF INTUSSUSCEPTION

Age	Ileo-colic*	Ileo-ileal	Other and Unknown Types	Total
0–8 mos.	51.1	57.1	75.0	55.4
	(131)	(7)	(28)	(166)
9 mos. and over	74.7	83.3	82.6	77.7
	(83)	(24)	(23)	(130)
Total	60.3	77.4	78.4	65.2
	(214)	(31)	(51)	(296)

* Includes ileo-caecal.

at 5 months (Perrin and Lindsay, 1921; Close, 1931) or 6 months (Fitzwilliams, 1908; Hipsley, 1935; Wakeley and Atkinson, 1938). It should be noted that in the present material age is calculated from date of birth, and a child aged 4 months and 29 days is classified as aged 4 months, although his age might well appear as 5 months in the hospital record.

The sex ratio at different ages is given in the final column of Table 3. Below the age of 9 months, males are only slightly in excess of females (55.4%); after 9 months the excess is very marked (77.7%). The difference in sex ratio between these two periods is significant (22.3 ± 5.6). For the ileo-colic variety alone this trend is also present (difference 23.6 ± 6.9). Numbers of cases of the ileo-ileal type are small, but it appears to differ from the ileo-colic variety in two respects: (a) age of patient is higher (77% over 9 months as compared with 39% in the ileo-colic series); and (b) sex ratio is higher (77.4% male as compared with 60.3%). The difference in sex ratio can be

attributed at least in part to the fact that ileo-ileal intussusceptions occur predominantly in the age period when intussusceptions of all types show a high sex ratio. Whether ileo-ileal cases also show a real increase in sex ratio independently of this age effect, as suggested in Table 3, cannot be determined on the numbers of cases available.

SEASONAL INCIDENCE

Previous reports on seasonal incidence of intussusception are conflicting. Bolling (1923) suggested that the condition was most common in the summer months; Close (1931) confirmed this finding for younger children, but found that after 1 year of age the condition was most common in the months December–March. High incidence in March and December was suggested by Fitzwilliams (1908) and in April and January by Perrin and Lindsay (1921). Hogg and Donovan (1946) and Hipsley (1935) found little or no seasonal variation. The present material is in agreement with the last observations. Table 4 shows no evidence of seasonal variation.

BIRTH WEIGHT

It has been frequently stated, without numerical evidence, that intussusception affects particularly children who are heavier or more well nourished than average. Weight at the time of illness is not available in the present series, but birth weight is known for 259 patients. Comparison of their birth weight with that of all births in

TABLE 4.—DISTRIBUTION OF AFFECTED ACCORDING TO MONTH OF OPERATION

Month of Operation	Patients Aged 0–8 Months			Patients Aged 9 Months and Over			Total		Total*
	Male	Female	Total	Male	Female	Total	Male	Female	
Jan–March	20	17	37	23	6	29	43	23	66
April–June	26	14	40	33	9	42	59	23	82
July–Sept	26	21	47	19	10	29	45	31	76
Oct–Dec	20	22	42	26	4	30	46	26	72
Total	92	74	166	101	29	130	193	103	296

* $\chi^2 = 1.8$, $n = 3$, $0.5 < p < 0.7$.

TABLE 5.—PERCENTAGE DISTRIBUTIONS ACCORDING TO BIRTH WEIGHT

Birth Weight (lb)	Affected		Birmingham Births, 1947	
	Male	Female	Male	Female
5 or less	3.0	8.6	8.8	11.2
6	25.3	31.2	20.5	25.9
7	34.3	40.9	34.9	36.2
8	26.5	16.1	24.5	20.0
9 or more	10.8	3.2	11.3	6.7
Total	99.9	100.0	100.0	100.0
No. of observations	166	93	11,602	10,811

Birmingham in 1947 (Table 5) suggests that at birth children with intussusception are of average weight. Hogg and Donovan (1946) noted that most patients fell within the normal weight limit for age and height.

BIRTH RANK AND MATERNAL AGE

The possibility of association between incidence and either birth order or maternal age has not previously been examined. Wakeley and Atkinson (1938) reported that 64 per cent of 121, and Hogg and Donovan (1946) 45 per cent of 123, patients were first born. Ravitch and McCune (1950) on the other hand considered that a surprising number of patients occupied the higher birth ranks.

In the present material both birth rank and maternal age were known for the 212 interviewed patients and for the 30 additional patients whose birth certificates were found. Birth rank alone was available from the original hospital record for an additional 33 patients. The sample of all births in Birmingham originally assembled by Record and McKeown (1949) was completed in respect of the years 1942–52 by Smith and Record (1955). The sample as now used was modified from the latter by (a) inclusion of additional years (1953–54) and (b) exclusion of years 1942–44 and of all stillbirths. It is in effect a $\frac{1}{200}$th sample of all livebirths during the period 1945–54.

Distributions of the intussusception series and comparison sample are compared with respect to birth rank in Table 6 and to maternal age in Table 7. There are no significant differences. The independent effects of the two variables are examined in Table 8. To arrive at the estimates of incidence in different birth ranks and maternal ages it was assumed that (a) all livebirths in the city are distributed in the

TABLE 6.—DISTRIBUTION ACCORDING TO BIRTH RANK

Birth Rank	Affected		Comparison Group		Difference Between Percentages
	Number	Per cent	Number	Per cent	
1	106	38.55	335	32.81	+5.74 ± 3.22
2	83	30.18	343	33.59	−3.41 ± 3.19
3	43	15.64	154	15.08	+0.56 ± 2.44
4	17	6.18	91	8.91	−2.73 ± 1.88
5 and over	26	9.45	98	9.60	−0.15 ± 2.00
Total	275	100.0	1021	100.0	—

TABLE 7.—DISTRIBUTION ACCORDING TO MATERNAL AGE

Maternal Age (years)	Affected		Comparison Group		Differences Between Percentages
	Number	Per cent	Number	Per cent	
Under 20	8	3.31	53	5.19	−1.88 ± 1.53
20–24	56	23.14	247	24.19	−1.05 ± 3.05
25–29	81	33.47	319	31.24	+2.23 ± 3.33
30–34	54	22.31	233	22.82	−0.51 ± 3.00
35–39	33	13.64	131	12.83	+0.81 ± 2.40
40 and over	10	4.13	38	3.72	+0.41 ± 1.34
Total	242	100.0	1021	100.0	—

TABLE 8.—INCIDENCE OF INTUSSUSCEPTION (PER 1000 LIVEBIRTHS) ACCORDING TO BIRTH RANK AND MATERNAL AGE

Birth Rank	Maternal Age (years)						Total
	Under 20	20–24	25–29	30–34	35–39	40 and over	
1	1.12	1.82	1.90	1.45	2.25		1.72
2	0.88		1.39	2.12	0.59		1.32
3	0.82		2.01	1.09	2.17		1.55
4	—	0.87		0.61	1.62		1.04
5 and over	—	—	1.05	1.22	1.61	2.52	1.60
Total	0.95	1.43	1.60	1.45	1.59	1.66	1.49

same way as the comparison sample, and (b) untraced patients with intussusception are distributed in the same way as those traced. There is no consistent trend with birth order. Incidence may increase slightly with increasing maternal age, but the association is not constant and the results are no more than suggestive.

Results were also negative when the association of incidence with age and parity was examined separately (a) for ileo-caecal and ileo-ileal intussusceptions and (b) for patients under and over 9 months of age.

INCIDENCE IN SIBS

There were four fraternities in which two members were propositi in the present series, and a further four in which a sib born before the first propositus was affected. Some details of these eight fraternities are given in the appendix. Close (1931) found 5 instances of affected sibs in 146 reports, and Hogg and Donovan (1946) reported 3 cases among relatives of 123 patients.

For an estimate of the risk to sibs of an affected individual, attention is confined to the 209 families (containing 212 propositi) traced by field enquiry. These families include 3 with 2 propositi and 3 with an affected previous sib. An estimate of the risk to sibs can be obtained in two ways:

(a) By ignoring previous sibs and confining attention to sibs born after the first propositus. There were 128 such sibs, of which 3 (1 in 43) were affected.

(b) By using data for all family members and making the corrections described by Hogben (1931) for family size and the fact that fraternities are selected by the presence of at least one affected member. This procedure is followed in Table 9, the estimate of risk to siblings obtained in this way being 0.029 or approximately 1 in 34.

The results of both methods suggest that the risk to sibs is about 1 in 40, or between 15 and 20 times the incidence in the general population.

Numbers are very small, but examination of the appendix does not suggest that recurrence in a fraternity is associated with age or sex. With one exception, all the familial cases are ileo-caecal or ileo-colic in type, but this type accounts for 84 per cent of all cases.

Other affected relatives reported by the 209 interviewed mothers were maternal cousin (3), paternal cousin (3), mother's cousin (3), paternal uncle (2) and maternal

TABLE 9.—RISK OF INTUSSUSCEPTION IN SIBS OF PROPOSITI

Family Size	Number of Families	Number of Children	Number of Affected Children	
			Observed	Expected* r = 0.029
1	40	40	40	40.00
2	69	138	70	69.97
3	38	114	40	39.12
4	28	112	29	29.23
5	11	55	13	11.66
6	12	72	12	12.90
7	7	49	7	7.63
8	2	16	2	2.21
9	1	9	1	1.12
10	1	10	1	1.14
Total	209	615	215	214.98

* Calculated from the formula $p = \frac{r}{1 - (1 - r)^s}$, where p = proportion affected, r = risk to siblings and s is family size.

uncle (1). No parents were affected. Hipsley (1935) states that he has seen a family in which father and child both had intussusception in infancy. The number of other relatives "at risk" is unknown, but in a previous enquiry into the familial incidence of pyloric stenosis in the same area (McKeown, MacMahon and Record, 1951) it was found that there were on average about 8 cousins to each propositus. On this basis about 2 affected cousins would have been expected in the present material. There were 6, but numbers are too small to justify the conclusion that incidence in cousins is raised.

SUMMARY

Survey of the records of all pediatric and general hospitals in the City of Birmingham, England, for the years 1945–54 revealed 296 confirmed cases of intussusception in Birmingham children under the age of ten years. In addition to data in the hospital record, information was obtained for 212 cases by interview with the mother during 1955, and from birth certificates of a further 30 patients who could not be traced in 1955.

The incidence of the condition was 1.49 per thousand livebirths. 65.2% of the patients were less than 1 year of age, the modal age being 4 months. Below the age of nine months males were only slightly in excess of females (55.4%); after nine months the excess was very marked (77.7%). Differences in age and sex distribution between the ileo-ileal and ileo-colic types were noted.

No significant evidence of the influence of season, birth weight, birth rank or maternal age was found.

There were eight fraternities in which two members were affected. The risk to sibs of an affected individual is estimated as about 1 in 40, or between 15 and 20 times the incidence in the general population.

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For access to case records I am indebted to the medical and administrative staffs of all Birmingham hospitals, in particular of the Children's Hospital. I am grateful to Miss Ida Giles who interviewed the mothers in their homes.

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APPENDIX.—DETAILS OF 8 FAMILIES IN WHICH 2 CHILDREN HAD INTUSSUSCEPTION

No. of Family	Date of Mother's Birth	Birth Rank of Child	Date of Birth	Sex	Age at Operation	Type of Intussusception
1	6/8/17	1*	11/7/44	M	6 mos.	Ileo-colic
		2*	20/1/50	M	12 mos.	Ileo-caecal
2	23/6/20	1	1/8/41	F		
		2	6/8/43	M		
		3*	2/2/45	F	8 mos.	Ileo-colic
		4	2/2/49	M		
		5*	8/7/52	M	3 mos.	Caeco-colic
3	12/2/24	1*	30/5/46	M	3 mos.	Not stated
		2	11/8/48	F		
		3*	16/1/50	M	3 mos.	Ileo-colic
4	25/12/22	1†	18/2/43	M	5 mos.	Ileo-colic
		2	23/11/47	M		
		3*	20/12/52	M	4 mos.	Ileo-colic
5	7/3/13	1	12/4/35	M		
		2†	29/7/42	F	5 mos.	Not stated
		3*	30/12/44	M	1 yr 11 mos.	Ileo-caecal
		4	15/9/45	F		
6	5/10/06	1†	2/8/31	F	5 mos.	Not stated
		2	29/3/36	M		
		3	18/7/37	F		
		4	30/4/47	M		
		5*	6/2/50	F	3 mos.	Ileo-caecal
7	?	1*	7/3/48	M	3 mos.	Ileo-colic
		2	? ? 50	F		
		3*	1/9/52	F	10 mos.	Ileo-caecal
8	?	1†	?	?	4 mos.	?
		2*	1/3/46	F	4 mos.	Ileo-caecal

* Indicates a propositus, and † an affected child, not a propositus. Families 7 and 8 were not traced by field enquiry, and are omitted for the purposes of estimating incidence in sibs (see text)

BOOK REVIEWS

Lethalfaktoren in ihrer Bedeutung für Erbpathologie und Genphysiologie der Entwicklung

By ERNEST HADORN, Stuttgart, Georg Thieme Verlag, 338 pp., 129 illustr. $9.30.

THE main title of this book, "Lethals", may at first suggest a dry enumeration of the kinds and effects of the many conditions which cause genetic deaths of various organisms. The subtitle, however, quickly indicates the deeper aspects of the treatment of lethals "in their significance for pathological genetics, and physiological genetics of development." The author, well known for his extensive and original investigations of the general experimental embryology of vertebrates and insects as well as in the genetic, developmental and biochemical analysis of lethals in Drosophila has here brought together the results of the manifold studies on lethality and abnormal development which have been published by numerous workers over the decades. Clearly and thoroughly the material is presented under headings appropriate to the physiological and developmental viewpoint which characterizes this monograph.

The first third of the book deals with the more narrowly genetic aspects such as methods of discovering lethals, breeding methods for keeping lethals in stock, the origin of lethals by mutation and the chromosomal bases of lethal mutations. These chapters are informative and well balanced but will be of use primarily to those who have not obtained their knowledge of these topics from other sources. Hadorn's peculiar strength expresses itself in the chapters on penetrance and expressivity, on phase-specificity of action where the killing effects of different genes are shown to be either restricted to single developmental stages or to two or more, on cell and organ specificity of action, on the pleiotropic action and damage pattern, on transplantation and explantation work destined to delineate cellular autonomy or interdependence of lethal action, on the facts and interpretations of phenocopy experiments, on biochemical effects of lethals and on the physiology of abnormal development. "General remarks on developmental standstill and anormogenesis as consequences of mutations" close the main part of the book. They are followed by several pages of definitions, a very valuable list of literature cited (over 600 titles), and subject and author indexes.

An important feature of the book is the many excellent illustrations all specially prepared, though of course often based on figures or data of other authors. The paper and typography are of best quality. The size of the page is large so that the content of the 338 pages would easily fill 500 pages of a book of usual format.

The human geneticist will learn much to direct his thinking into dynamic ways. He may find useful the term "phene" which designates any one specific trait assigned to a gene, and the subterms "autophene" and "allophene" which respectively refer to a phene caused by the genetic constitution within the cells themselves which show the phene or one dependent on the genotype of another cell system of the individual. He will profit from the detailed discussions of various types of expression of lethals in different genetic backgrounds and as influenced by maternal effects. He will be impressed by Hadorn's demonstration of the phenomenon of "Durchbrenner", those individuals of "lethal" genotypes who manage to survive their critical phase and, so to say, run away successfully from their supposed fate.

The need for integration of genetic concepts and tools into the field of development has

long been stressed by a relatively small number of biologists. Hadorn's book is a lasting contribution toward this goal.

CURT STERN
University of California, Berkeley

Genetics and Metabolism

By ROBERT P. WAGNER (University of Texas) and Herschel K. Mitchell (California Institute of Technology) New York: John Wiley & Sons, Inc. 1955. Pp. 444. $7.50.

ONE significant trend in recent scientific advances has been the correlation of genetical and biochemical observations. Such work has involved geneticists, biochemists, and microbiologists, each lending his own field of speciality to the over-all problem. Because of the diversity of subject matter in these areas of science, a comprehensive coverage of the significant information pertaining to genetics and metabolism constitutes a valuable contribution to science. This book effectively unites the facts available in the literature to formulate some fundamental concepts and aid in unifying the various approaches to the subject. The authors planned and wrote the book around the thesis . . . "that inheritance is characterizable in terms of transmission of control of relative rates of biochemical reactions within complex and interlocked metabolic patterns".

Several of the broad concepts formulated in this book are subject to controversy. However, this should not be considered as a criticism of the book since many gaps exist in the factual knowledge needed for a complete concept. In addition the emphasis of the importance of enzyme kinetics in complex interrelated *in vivo* systems rather than in isolated *in vitro* systems places the book contents in a nebulous area which has not been properly developed to date. It must be admitted that the final solutions to genetical problems must come from *in vivo* studies, and this book does much to point the way for future attacks on such problems. The only specific criticism of this book is that it contains many clumsy sentence structures.

Genetics and Metabolism was primarily written for advanced undergraduates or graduate students in the fields of genetics, microbiology, or biochemistry. It is assumed that the reader will have a background of elementary biology, genetics, and biochemistry. However, elementary facts of these subjects are included where pertinent throughout the book in order to make the contents more accessible to more individuals and to crystallize the necessary knowledge in these fields for the reader. This book should also be of value to scientists in the three fields involved since it will be of aid in broadening basic concepts and will familiarize the reader with significant advances which may be out of this realm of study.

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Investigations on Genetic Aspects of Carcinoma of the Stomach and Breast

By CHARLES M. WOOLF. University of California Publications in Public Health 1955, 2: 265–350. 5 figures.

THIS excellent monograph reports work which was done as a doctoral thesis. Two hundred families were studied for the breast cancer work and the same number for gastric cancer. The original patient dying with either of these cancers was selected from the death records of Utah in years from 1940 to 1950. Their parents and sibs were then studied for the fre-

quency of breast and gastric cancer respectively. The method of proportionate death rates was used, comparing the frequency of breast and stomach cancer in the relatives of the breast and stomach cancer patients with the frequency of these two types of cancer in the population of Utah of the same sex, age-range and date-of-death distribution. In the case of gastric cancer, 44 stomach cancers were found in the relatives whereas only 25.26 were expected, the P value being less than 0.001. Other types of cancers were found in these relatives however, in about the amount expected, 67 being observed and 72.8 expected. The P value was between 0.3 and 0.5.

The spouses of gastric cancer patients had 18 gastric cancers and 18.2 were expected, showing that unrelated persons sharing the same environment throughout a large part of their adult lives did not have the same type of cancer any oftener than would be expected on the basis of random distribution.

Breast cancer occurs for the most part in the female sex only, and hence the number of cancers found was smaller than in the case of gastric cancer. Twelve breast cancers were found and only 5.27 were expected, again showing a significant excess; the P value here being less than 0.01. The amount of other cancers found was well within the expected range. Woolf concludes that a definite genetic component is present in both of these cancers but that quantitatively the effect is small, exogeneous factors being of greater etiological importance. No simple pattern of inheritance was noted and he postulated that in these two cancers, as in certain types of mouse carcinoma multiple genetic and non-genetic factors are involved. The cancer develops when the combined effects of the genetic and non-genetic components surpass a critical physiological threshold.

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Counseling in Medical Genetics

By SHELDON C. REED (Dight Institute, University of Minnesota). W. B. Saunders Company, Philadelphia, 1955, viii + 268, $4.00.

ONE of the most obvious applications of genetical knowledge to medicine is the estimation of likelihood of hereditary disease in the offspring of prospective parents. Traits, which can be identified with precision in heterozygotes or hemizygotes, can supply the data for exact prediction. With recessive traits the situation is often less clear and involves knowledge of gene frequencies and information about consanguinity. In the Dight Institute for Human Genetics, attached to the University of Minnesota, of which Dr. Sheldon C. Reed is the director, the commonest requests, from parents for advice, concern traits, whose genetics are at present undetermined, for example, skin colour, epilepsy, mongolism, schizophrenia, harelip and cleft palate, eye colour and twinning. The study of Mendelism as applied to man and an understanding of the Hardy-Weinberg law are necessary but insufficient as a basis on which to make judgments on these matters. It is extremely difficult to give correct advice in the great majority of cases which present themselves for genetical counseling. Indeed some experienced human geneticists believe that the main value of such counsel is to allay unreasonable anxiety and is therefore psychiatric treatment for the prospective parent rather than eugenical treatment for the offspring. A medical technique with so many aspects could be well served by an authoritative and serious treatise though the labour involved in compiling existing knowledge in a useful and critical manner would be immense. In *Counseling in Medical Genetics*, Dr. Reed has made an attempt to cover the field in so far as it concerns the problems which have arisen most commonly in practice. He writes as a layman and a geneti-

cist to help the physician to answer his patients' questions concerning heredity. It is natural to enquire how far this book is likely to achieve its purpose.

The list of topics described in the table of contents is, at first glance, impressive. Congenital malformations, like harelip, heart defect, pyloric stenosis, dislocation of the hip and club foot, are all discussed after dealing with mongolism, anencephaly and spina bifida. Allergy, diabetes and the psychoses are also strongly represented. The chapters on all these subjects include a quantity of information useful for the purpose intended and usually obtained from reliable sources. The style of writing, however, is hurried and not always clear; e.g. (p. 164) 'The disease is often accompanied by mental deficiency or vice versa.' Logical argument is not a strong point. Mongolism (p. 50) is said to be a progressive disease. 'This is evidence', says the author, 'that the defect is within the Mongoloid child and not imposed upon it by the mother.' The same argument might be applied to congenital syphilis.

When the illustrative descriptions of counseling are examined, doubts arise as to the competence of the author to set an example to others. It is difficult to believe that these anecdotes can be intended to serve as standard patterns. See, for instance, the advice given to an asthmatic (p. 188, which ends with the prediction that 'medical research should come to your aid within the next few years with injections which will be much more powerful than those now known.' The worst features of the book are the chapters, like that on 'String beans and chubbies', in which the writer allows himself to be carried away by a kind of journalistic frivolity quite incompatible with serious application of scientific human genetics to medicine: it would be a waste of time to discuss them in detail. It is regrettable that a book, which promises so much by its title and its preface, should be found, on examination, to be so inadequate.

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LETTERS TO THE EDITOR

June 29, 1955

To the Editor
Dear Sir:

In their article on Microcephaly, Komai, Kishimoto and Ozake (*Amer. J. Hum. Genet.* 7: 51–65, 1955) make an estimate of the gene incidence for this disease by using the formula

$$q = \frac{c(1 - k)}{16k - 15c - ck} \tag{1}$$

where q is the incidence, k the proportion of the microcephalics whose parents were first-cousins and c the proportion of first-cousin matings among the population in general. Although this formula is called DAHLBERG's formula, I was unable to find it in this author's papers quoted by Komai et al. Obviously it is derived from the formula

$$k = \frac{c}{c + \dfrac{1/16q(k - c)}{1 + 15q}} \tag{2}$$

It seems quite clear, however, that Dahlberg (*Mathematical Methods for Population Genetics*, Basel 1947; *Advances in Genetics* 2: 269–298, 1948) favours another formula which takes into consideration the fact that in a given population there might be a difference between the cousin matings that actually occur, c_1, and the frequency with which such marriages are to be expected in panmixia, c_2. This formula runs as follows,

$$k = \frac{c_1}{c_1 - c_2 + \dfrac{16q(1 - c_1 + c_2)}{1 + 15q}}$$

and from it we can derive

$$q = \frac{c_1 - k(c_1 - c_2)}{16k(1 - c_1 + c_2) - 15\,[c_1 - k(c_1 - c_2)]} \tag{3}$$

If we assume that the population is so large that the random frequency of cousin marriages to be expected is small enough to be ignored, i.e., $c_2 = 0$, we get formula (1). If, on the other hand, we assume that the difference between c_1 and c_2 is small enough to be ignored, i.e., if $c_1 = c_2 = c$, formula (3) becomes

$$q = \frac{c}{16k - 15c} \tag{4}$$

Let us call the value q given by formula (1) q_1 and that given by (4) q_4. Then, for the same values of c and k a substantial difference is found between q_1 and q_4 as shown in table 1.

A look at this table also shows that the difference between q_1 and q_4 is increasing with decreasing gene-frequencies. In other words the difference becomes important for rare diseases. This is interesting as Microcephaly obviously is a rare disease, k being as large as 44.8% in the material used by Komai et al. We have calculated the frequency of the gene for Microcephaly using formula (4) and the figures obtained are given together with those of Komai et al. in table 2. It is seen at once that the differences are considerable.

Komai et al. claim that there is a good agreement between their estimation and that of Böök et al. (*Amer. J. Ment. Def.* 57: 637–660, 1953) who found the incidence of the gene for Microcephaly

TABLE 1

k	q_1	q_4
0.634	0.00036	0.001
0.072	0.0093	0.01
0.0153	0.105	0.1
c = 0.01		

TABLE 2

k = 0.448		
c	q_1	q_4
0.04	0.0034	0.00609
0.05	0.0043	0.00779
0.06	0.0053	0.00958
0.07	0.0063	0.01144

in the Swedish population to be between 0.0043 and 0.0062. This statement however, does not bear out their previous claim (1955, p. 51) "that microcephaly of genetic origin is apparently more common among Japanese than among occidental peoples." More consistent with it are, however, the values obtained with formula (4).

In view of these facts we may say in conclusion:

1) that Komai et al. made use of a formula which is probably not the most correct one and

2) that the incidences of the gene for Microcephaly are consequently open to criticism and must be checked before they can be accepted.

Sincerely yours,

R. DERAEMAEKER, M.D.
Vlaamse Kunstlaan 64
Antwerp, Belgium

July 13, 1955

To the Editor
Dear Sir:

The methods for calculating the variances, and thus the standard deviations, of the gene frequencies, as estimated by my method for MNS data (*Amer. J. Hum. Genet.* 6: 1–10, 1954) are unfortunately incorrect as given. The method of estimating the gene frequencies, which itself is perfectly correct in its results, depends essentially, as does the Rh method published later (Boyd 1954b), upon the estimation of certain sums of gene frequencies by direct gene counting, then the estimation of the fractions of these sums which make up the various gene frequencies. From MNS data total m and total n are estimated by counting, and the gene frequencies m_s, m_S, n_s, and n_S are determined if g and d are known, where $m_s = gm$, $m_S = (1 - g)m$, $n_s = dn$, $n_S = (1 - d)n$. The simplification introduced by this method depends upon the fact that the likelihood expression can be factored into two separate expressions, one involving only m and n and the other involving only g and d. The latter now involves only two independent unknowns instead of three. All this the reader will readily be able to verify.

The error in the estimates of the variances arises from the fact that the elements of the information matrix, called incorrectly $I_{m_g m_g}$, $I_{n_g n_g}$, etc. are really $(1/m^2)I_{gg}$, $(1/n^2)I_{dd}$, etc., because of a factor of 1/m which results when the likelihood expressions are differentiated. This is readily shown

by working out all the expressions in terms of g and d. Therefore the elements of the reciprocal variance matrix are really m^2V_{gg}, n^2V_{dd}, etc., their square roots do not give the standard deviations of m_s and n_s, and the formulas derived for me by Dr. Levene for the variances of m_S and n_S, although perfectly correct, do not apply. Instead the following formulas are needed:

$$V_{m_s} = \text{“}V_{m_s m_s}\text{”} + m_s^2 n/2mG \qquad V_{m_S} = \text{“}V_{m_S m_S}\text{”} + m_S^2 n/2mG$$
$$V_{n_s} = \text{“}V_{n_s n_s}\text{”} + n_s^2 m/2nG \qquad V_{n_S} = \text{“}V_{n_S n_S}\text{”} + n_S^2 m/2nG$$

where the expressions in quotation marks are the elements of the variance matrix (really m^2V_{gg} and n^2V_{dd}) as found by the methods of the paper referred to (Boyd 1954a), and the other symbols have the same meaning as before. Using these formulas we obtain for the correct variances

$$V_{m_s} = 7.2637 \times 10^{-4} \qquad V_{m_S} = 5.6258 \times 10^{-4}$$
$$V_{n_s} = 6.4461 \times 10^{-4} \qquad V_{n_S} = 4.4419 \times 10^{-4}$$

The correct standard deviations, somewhat larger than those originally given, are therefore $\sigma_{m_S} = 0.02695$, $\sigma_{m_S} = 0.02372$, $\sigma_{n_S} = 0.02539$, $\sigma_{n_S} = 0.02108$.

It should be emphasized that this error affects only the estimates of the variances. The method of estimating the gene frequencies is perfectly satisfactory as outlined (Boyd 1954a), and requires no alteration. The methods of estimating the variances given in my Rh paper (*Amer. J. Hum. Genet.* 6: 303–318, 1954) require no correction.

Sincerely yours,

WILLIAM C. BOYD,
Boston Univ. School of Medicine

August 31, 1955

Sehr verehrter Herr Snyder:

In dem letzten Heft 2, Volume 7, vom Juni 1955 ist auf Seite 218/219 eine Besprechung von Alexander S. Wiener uber das Buch von H. Schade “Vaterschaftsbegutachtung” erschienen.

Wiener beginnt seine Besprechung mit den beiden Sätzen: “During World War II many families were separated. After the war, families were reunited, but due to the passage of many years not infrequently uncertainties as to parentage arose. This situation in Germany was the inspiration for this book.”—*Richtig* ist, dass im Jahre 1945 viele hunderttausende von deutschen Familien getrennt wurden. Der Suchdienst des Roten Kreuzes hat zehntausende von elternlosen Kindern ihren Eltern wieder zugeführt. In einigen wenigen dieser Fälle hat ein wissenschaftliches Gutachten eine Hilfe gegeben.—*Falsch* ist jedoch, dass diese Situation “the inspiration” für das Buch von H. Schade war. Denn wie aus meinem Geleitwort und der Einleitung des Autors entnommen werden kann, ist die anthropologisch-erbbiologische Vaterschaftsbegutachtung in Deutschland seit dem Jahre 1928 in Gebrauch. Seit langem bestand das Bedürfnis nach einer buchmässigen zusammenfassenden Darstellung, das erst durch Herrn Schade erfüllt worden ist.

Falsch ist, wie Wiener meint, dass Schade “is dissatisfied with blood tests” und dass er deshalb versucht habe “to find other methods.” *Richtig* ist und wird von Schade klar zum Ausdruck gebracht, dass das *serologische* Gutachten auch bei uns in Deutschland weitgehende Anwendung findet. Nur die *danach* noch verbleibenden Fälle von strittiger Vaterschaft werden durch das anthropologisch-erbbiologische Gutachten zu klären versucht. Nur auf diese zweite Etappe der Begutachtung bezieht sich das Buch von Schade. Er will also *keinen Ersatz* für die serologische Methode geben, sondern eine *Ergänzung für ungeklärt verbliebene Fälle.*

Wiener bemängelt, dass “only nine pages are devoted to the entire field of blood grouping.” Über die serologische Vaterschaftsbegutachtung gibt es bereits gute buchmässige Darstellungen. Bei der anthropologischerbbioloischen Vaterschaftsbegutachtung handelt es sich um eine ergänzende Untersuchung, die auf das Ergebnis der serologischen Untersuchung aufbaut.

Falsch ist, wie Wiener meint, dass die von Schade dargestellte Methode begründet sei “on external measurements of the body.” An anderer Stelle spricht Wiener von “the hundreds of measurements”.

Richtig ist, dass die körperlichen masse nur eine der 12 in abschnitt F des Buches behandelten Merkmalsgruppen sind. Auch aus dem in dem Buch wiedergegebenen Untersuchungsbogen geht hervor, dass die 17 Kopfmasse und 14 Körpermasse nur einen kleinen Teil der Gesamtuntersuchung ausmachen. Das Gutachten stützt sich vielmehr ganz wesentlich auf den morphologischen Vergleich in Merkmalen, deren vorwiegende Erbbedingtheit durch Zwillings- und Familienuntersuchungen bekannt ist.

Wiener meint richtig "The reviewer would like to see Prof. H. Schade subjected to a blind test, in which Prof. Schade would be requested to examine and measure parents and children whose relationships are known but kept secret from him, and then let him decide which children belong to which parents". Jeder in der anthropologisch-erbbiologischen Vaterschaftsbegutachtung erfahrene Humangenetiker wird sich zu solch einem "blind test" gerne zur Verfügung stellen. Die Voraussetzung ist allerdings—wie für jede erbbiologische, auch für die serologische Vaterschaftsfeststellung—dass Mutter und Kind sich in eindeutig feststellbaren Merkmalen unterscheiden.

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